

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216483Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	216483
Priority or standard	Priority
Submit date(s)	10/24/2023
Received date(s)	10/24/2023
PDUFA goal date	4/24/2024
Division/office	Division of Anti-Infectives (DAI)
Review completion date	4/10/2024
Established/proper name	Pivmecillinam
(Proposed) proprietary name	PIVYA
Pharmacologic class	Penicillin class of antibacterial
Other product name(s)	PIVYA (pivmecillinam)
Applicant	Utility Therapeutics, LTD
Dosage form(s)/formulation(s)	Oral Tablet
Dosing regimen	185 mg three times a day for 3 to 7 days.
Applicant-proposed indication(s)/population(s)	<i>Treatment of adults with uncomplicated urinary tract infections (uUTI) caused by susceptible (b) (4) and Staphylococcus saprophyticus</i>
SNOMED CT code for proposed indication disease term(s)¹	4009004 Lower urinary tract infectious disease (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	One 185 mg tablet orally 3 times a day for 3 to 7 days
Approved indication(s)/population(s) (if applicable)	<i>Treatment of female patients 18 years of age and older with uncomplicated urinary tract infections (uUTI) caused by susceptible isolates of Escherichia coli, Proteus mirabilis, and Staphylococcus saprophyticus</i>
SNOMED CT code for approved indication disease term(s)^a	4009004 Lower urinary tract infectious disease (disorder)

^a For internal tracking purposes only.

Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BA	bioavailability
BID	twice daily
BLA	biologics license application
BP	binding protein
CDER	Center for Drug Evaluation and Research
CFU	colony-forming unit
CIP	ciprofloxacin
CL	clearance
CLSI	Clinical and Laboratory Standards Institute
C _{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CrCl	creatinine clearance
CRF	case report form
cUTI	complicated urinary tract infection
DD	disk diffusion
DDI	drug-drug interaction
ESBL	extended spectrum beta-lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
FOF	fosfomicin
GD	gestation day
GLP	good laboratory practice
HCL	hydrochloride
HPLC	high-performance liquid chromatography
IC ₅₀	half maximal inhibitory concentration
IND	investigational new drug
ISE	integrated summary of effectiveness
ITT	intent-to-treat
IV	intravenous
IVA	isovaleric acidemia
LD	lactation day
MEC	mecillinam
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
micro-ITT	microbiological intent-to-treat
NBS	newborn screening
NDA	new drug application
NI	noninferiority
NIT	nitrofurantoin

NDA 216483
PIVYA (pivmecillinam)

NOAEL	no observed adverse effect level
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigations
PBP	penicillin binding protein
PCA	pivalate-conjugated antibacterials
PD	pharmacodynamic
PI	Prescribing Information
PIND	pre-investigational new drug
PIV	pivmecillinam
PK	pharmacokinetic
PMC	postmarketing commitment
PO	orally
PopPK	population pharmacokinetic
PPB	plasma protein binding
PSUR	periodic safety update report
PT	preferred term
PTA	probability of target attainment
QC	quality control
QID	four times daily
QIDP	Qualified Infectious Disease Product
SAE	serious adverse event
SAP	statistical analysis plan
SCR	serum creatinine
STIC	susceptibility testing interpretive criteria
TEAE	treatment-emergent adverse event
TID	three times daily
T _{max}	time to maximum concentration
TMP	trimethoprim
TOC	test-of-cure
UTI	urinary tract infection
uUTI	uncomplicated urinary tract infection

I. Executive Summary

1. Summary of Regulatory Action

New drug application (NDA) 216483 for pivmecillinam oral tablets was submitted by Utility Therapeutics Group Ltd. (Applicant) for the treatment of adults with uncomplicated urinary tract infections (uUTI). NDA 216483 was filed as a priority review classification NDA, and the Prescription Drug User Fee Act (PDUFA) goal date is April 24, 2024.

Pivmecillinam is a penicillin class antibacterial drug with activity against gram-negative bacteria including several species of Enterobacterales and *S. saprophyticus*. Pivmecillinam demonstrated in vitro and clinical activity against *Escherichia coli*, *Proteus mirabilis* and *Staphylococcus saprophyticus*.

(b) (4) Mecillinam (MEC) intravenous was approved in 1984 for uUTI and complicated urinary tract infection. (b) (4)

In the current NDA, the Applicant submitted legacy datasets of three randomized controlled studies of pivmecillinam in 369 adult females for the treatment of uUTIs at the proposed dose of 200 mg TID for 3 to 7 days, comparing pivmecillinam with placebo, ibuprofen, and cephalexin, respectively. The trials demonstrated the efficacy of pivmecillinam for the treatment of uUTI based on the composite response rates that included clinical cure and microbiological response, with confidence intervals in placebo-controlled or ibuprofen-controlled trials corresponding to highly statistically significant treatment effects.

The safety database for this NDA consisted of 579 subjects who received pivmecillinam at 200 mg TID daily for 3 to 10 days in a placebo-controlled trial, active controlled trial, and an open label trial, respectively. An additional 479 subjects received pivmecillinam at 400 mg BID for 3 days in an active-controlled study. Pivmecillinam is marketed outside the U.S and available safety data were taken into consideration. No unexpected safety signals were identified during the development program. The safety profile appears generally consistent with other pivoxil-conjugated beta-lactam drug products.

Based on review of the available efficacy and safety data, NDA 216483 for pivmecillinam provides substantial evidence of effectiveness and a favorable benefit-risk profile for the treatment of female patients 18 years of age and older with uUTI caused by *E. coli*, *P. mirabilis*, and *S. saprophyticus*.

The drug product pivmecillinam (PIVYA) will be expressed at the strength of 185 mg, equivalent to 200 mg of pivmecillinam hydrochloride in the labeling. In this review, pivmecillinam and pivmecillinam hydrochloride were used interchangeably. For detailed information supporting the basis for this approval, please refer to the reviews included in this interdisciplinary assessment document and the product quality review.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	- Uncomplicated UTIs are characterized by pyuria and a documented microbial pathogen in urine culture, accompanied by local signs and symptoms such as lower abdominal discomfort, urinary urgency, urinary frequency and dysuria (August 2019). - By definition, uUTIs occur in females with normal anatomy of the urinary tract who are not at risk for complications such as immunocompromising conditions or poorly controlled diabetes, and do not have systemic signs or symptoms such as fever greater than 38°C or costovertebral angle tenderness (August 2019). - Urinary tract infections are the most common bacterial infections encountered in the ambulatory care setting in the United States, accounting for 8.6 million visits (84% by women) in 2007 (Hooton 2012). - uUTIs may have early resolution of symptoms (25 to 42%) (Ferry et al. 2007) but can rarely progress to cUTIs in the absence of antimicrobial therapy (Vik et al. 2018). - uUTI is one of the most common indications for antimicrobial therapy in otherwise healthy females. Risk factors include recent sexual intercourse, a history of UTI, and use of condoms, diaphragms, or spermicides. <i>E. coli</i> is the most frequent pathogen associated with uUTI. Other species of Enterobacterales, such as <i>K. pneumoniae</i> and <i>P. mirabilis</i>, and other bacteria such as <i>S. saprophyticus</i> are encountered less frequently. - uUTIs are often treated empirically without antibacterial susceptibility testing. Urine culture and susceptibility testing are recommended for subjects who are at risk for infection with resistant organisms or with risk factors for more serious infection,	uUTIs are associated with significant morbidity. Untreated or inadequately treated uUTIs are associated with prolongation of symptoms and may progress to cUTIs. Effective antimicrobial therapies alleviate the symptoms of uUTI, shorten the course of illness, and may prevent its progression to cUTI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	such as underlying urologic abnormalities and immunocompromising conditions.	
Current treatment options	- First line treatment options for uUTIs approved in the U.S. include nitrofurantoin, TMP-SMX, and fosfomycin. In countries where pivmecillinam is available, pivmecillinam 400 mg BID for 3 to 7 days is also recommended as an initial treatment (Gupta et al. 2011). - Due to concerns regarding the development of resistance and adverse reactions on tendons, muscles, joints, and nerves, fluoroquinolones, including levofloxacin and ciprofloxacin, are not recommended as first line therapy for uUTIs. Fluoroquinolones are also associated with QTc interval prolongation and several drug-drug interactions. In addition, resistance to quinolones is prevalent in some geographic areas. - If resistance to TMP-SMX exceeds 20% in the community, empiric use of this agent is not recommended (Walker et al. 2016). - Nitrofurantoin remains a recommended therapy due to low resistance patterns and a favorable safety profile. - Fosfomycin appears to have inferior efficacy compared to other standard short course regimens. - Nitrofurantoin is contraindicated in subjects with significant impairment of renal function (creatinine clearance <60 mL/min). In addition, TMP decreases tubular creatinine secretion and may increase serum creatinine. TMP-SMX is contraindicated in severe renal insufficiency when renal function cannot be monitored. TMP-SMX also has several drug-drug interactions with anticoagulants like warfarin causing elevation of prothrombin time and INR. TMP-SMX also has drug-drug interactions with diuretics, methotrexate and digoxin. - When other agents cannot be used, beta-lactams, including amoxicillin-clavulanate, may be appropriate, although they may be associated with more adverse events and lower efficacy than first line agents. - Cephalosporins may not be suitable for subjects with allergies or in subjects with documented resistance, e.g., ESBL-producing organisms. Use of broad spectrum cephalosporins and fluoroquinolones has been associated with selection of	Available treatment options for uUTIs have been limited by development of resistance and adverse reactions. As initial treatment of uUTIs is typically empiric, availability of effective treatment options with a favorable safety profile and low resistance among pathogens in the community is important.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	drug-resistant organisms and increased risk of uUTIs secondary to resistant organisms.	
Benefit	- The clinical efficacy of orally administered pivmecillinam for the treatment of uUTI caused by susceptible microorganisms was demonstrated in phase 3 clinical studies (Menday 2000; Ferry et al. 2007; Vik et al. 2018) in a total of 369 subjects administered pivmecillinam 200 mg three times a day for 3 to 7 days. - The primary efficacy endpoint was the composite response rate (composite endpoint of clinical cure and microbiological response) in the microbiological intent-to-treat (micro-ITT) population. - In Ferry 2007, composite response at TOC was achieved in 62% of subjects in the pivmecillinam group and 10% in the placebo group (Ferry et al. 2007). In Menday 2000, the composite response rate at TOC was 72% in subjects receiving pivmecillinam and 76% receiving cephalexin (Menday 2000). In Vik 2018, the composite response rate at TOC was 66% in the pivmecillinam group and 22% in the ibuprofen group (Vik et al. 2018). - Efficacy against pathogens producing extended spectrum beta-lactamases (ESBLs) could not be evaluated because this information was not collected in the efficacy studies. - Resistance rates to pivmecillinam were noted to be low in the efficacy studies. - No overall differences in effectiveness were observed between subjects 65 years of age and older and younger adult subjects in the Ferry and Menday studies; there were no subjects 60 years of age or older in the Vik study (Menday 2000; Ferry et al. 2007; Vik et al. 2018).	Substantial evidence of the effectiveness of pivmecillinam was demonstrated in clinical studies of adult females 18 years of age and older with uUTI. Demonstration of efficacy in pivotal studies was consistent across studies that enrolled subjects from 1984 and 2016 and in different geographical regions (USA, Norway, Sweden and Denmark). Pivmecillinam provides an additional oral option for treatment of uUTI caused by susceptible microorganisms.
Risk and risk management	- The safety database for pivmecillinam consisted of 579 subjects who received pivmecillinam at 200 mg TID for 3 to 10 days in a placebo-controlled study (Ferry et al. 2007), an active-controlled study, (Menday 2000) and one open-label study (Bresky 1977), with 14% of subjects being 65 years or older. An additional 479 subjects received pivmecillinam at 400 mg BID for 3 days in an active-controlled study (Nicolle et al. 2002). - There were no deaths or SAEs observed in the primary and supportive safety studies.	Overall, pivmecillinam was well tolerated, with an adverse reaction profile similar to other beta-lactam antibacterial drugs. No unexpected safety signals were identified during the review. The labeling includes warnings/precautions for serious hypersensitivity reactions, SCAR, carnitine depletion, porphyria, CDAD, development of drug-resistant

NDA 216483
PIVYA (pivmecillinam)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The most common adverse reactions observed in subjects treated with pivmecillinam included nausea and diarrhea. • Available safety data do not suggest a need for dosage adjustment in subjects with renal impairment, pregnant women, or the elderly. • There are limited studies on pivmecillinam use during pregnancy and the risk of miscarriage or other adverse maternal and fetal outcomes, which have limitations for interpretability. Published observational studies on pivmecillinam use during the first trimester do not indicate an increased risk of major birth defects. Postmarketing experience outside of the U.S. do not indicate an increased risk of congenital malformation or other adverse maternal or fetal outcomes. Of note, treatment of a pregnant individual with pivmecillinam prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of newborn screening. • There are insufficient data regarding the presence of mecillinam in human milk.	bacteria, and interference with a newborn screening test (i.e., for isovaleric acidemia). Pivmecillinam is not recommended when prolonged antibacterial treatment is necessary due to the risk of carnitine depletion. The Applicant is required to conduct a postmarketing study to evaluate for the presence of pivmecillinam in human breast milk and to assess for adverse effects in the breastfed infant.

Source: Clinical reviewer and CDTL

Abbreviations: AE, adverse events; CDAD, *Clostridioides difficile*-associated diarrhea; CDTL, cross-discipline team leader; cUTI, complicated urinary tract infection; ESBL, extended spectrum beta-lactamase; IDSA/ESMID, Infectious Diseases Society of America/European Society of Clinical Microbiology and Infectious Diseases; MEC, mecillinam; NI, noninferiority; SCAR, severe cutaneous adverse reactions; TMP-SMX, trimethoprim/sulfamethoxazole; uUTI, uncomplicated urinary tract infections

2.2. Conclusions Regarding Benefit-Risk

In NDA 216483 for pivmecillinam tablets, the Applicant is seeking an indication for treatment of adults with uUTI caused by susceptible (b) (4) and *S. saprophyticus*. Pivmecillinam is a penicillin class antibacterial drug with activity against gram-negative bacteria including several species of Enterobacterales, as well as the gram-positive bacterium, *S. saprophyticus*.

Uncomplicated urinary tract infection is one of the most common indications for antimicrobial therapy in otherwise healthy women, and currently recommended first-line treatments have been associated with rising resistance rates.

Clinical efficacy data in the NDA were provided from three randomized controlled studies of pivmecillinam in 369 adult females for the treatment of uUTIs at the proposed dose of 200 mg TID for 3 to 7 days compared to placebo ([Ferry et al. 2007](#)), ibuprofen ([Vik et al. 2018](#)) and cephalexin ([Menday 2000](#)). The primary efficacy endpoint was the composite response rate (composite endpoint of clinical cure and microbiological response) in the microbiological intent-to-treat (micro-ITT) population at test-of-cure. The trials demonstrated the efficacy of pivmecillinam for the treatment of uUTI based on the composite response rates that included clinical cure and microbiological response, with confidence intervals in placebo-controlled or ibuprofen-controlled trials corresponding to statistically significant treatment effects.

The NDA safety database consisted of 579 female subjects who received pivmecillinam at 200 mg TID for 3 to 10 days, including a randomized double-blind placebo-controlled study, a randomized double-blind active comparator (cephalexin) study, and a randomized open-label active comparator (amoxicillin) study ([Bresky 1977](#); [Menday 2000](#); [Ferry et al. 2007](#)). An additional randomized double-blind active comparator (norfloxacin) study evaluating pivmecillinam 400 mg twice daily for 3 days provided supportive safety data. No novel, unexpected safety signals were identified in the review ([Nicolle et al. 2002](#)). The safety profile of pivmecillinam appears consistent with other beta-lactam drug products.

Based on review of available efficacy and safety data, NDA 216483 provides substantial evidence and a favorable benefit-risk profile for pivmecillinam 200 mg TID for 3 to 7 days for the treatment of female patients 18 years of age and older with uUTI caused by susceptible isolates of *E coli*, *P. mirabilis*, and *S. saprophyticus*.

II. Interdisciplinary Assessment

3. Introduction

Uncomplicated urinary tract infection (uUTI) is one of the most common indications for antimicrobial therapy in otherwise healthy females and is characterized by pyuria and a documented microbial pathogen on urine culture, accompanied by local signs and symptoms such as lower abdominal discomfort and dysuria. Untreated or inadequately treated uUTIs are associated with prolongation of symptoms, and effective antimicrobial therapies can decrease the symptoms of uUTI and shorten the duration of illness.

E. coli is the most frequent pathogen associated with uUTI; other common pathogens include *K. pneumoniae* and *P. mirabilis*. Other bacteria such as *S. saprophyticus* are less frequently the cause. The incidence of infections caused by resistant gram-negative bacteria continues to rise, including urinary tract infection (UTI) caused by strains producing extended spectrum beta-lactamases (ESBLs). Use of broad spectrum cephalosporins and fluoroquinolones has been associated with selection of drug-resistant organisms and increased risk of uUTIs secondary to resistant organisms. Adverse events associated with other antibacterial drugs for uUTI such as fluoroquinolones and development of antibacterial resistance has limited the available treatment options.

Pivmecillinam hydrochloride, is a penicillin class antimicrobial with activity against gram-negative bacteria including several species of Enterobacterales and *S. saprophyticus*.

After oral administration pivmecillinam hydrochloride undergoes enzymatic hydrolysis releasing pivalate to form the active compound mecillinam (MEC). Pivmecillinam inhibits penicillin binding protein (PBP)-2, interfering with synthesis of the bacterial cell wall. (b) (4)

First approved in the UK in 1977, pivmecillinam has a long history of use outside the U.S. and is currently marketed in nine countries. On June 29, 2018, the FDA granted Qualified Infectious Disease Product designation to pivmecillinam hydrochloride (HCL) tablets for oral use for the treatment of uUTI.

The proposed indication is the treatment of adult females with uUTI caused by susceptible (b) (4) and

S. saprophyticus. The proposed dosage regimen is 200 mg pivmecillinam hydrochloride taken orally three times a day for 3 to 7 days as clinically indicated.

The efficacy of pivmecillinam for the proposed indication is supported by three clinical studies including a randomized, double-blinded study comparing pivmecillinam 200 mg TID for 7 days, 200 mg BID for 7 days and 400 mg BID for 3 days to placebo (Ferry et al. 2007), a multi-center, randomized, double-blinded, non-inferiority study comparing pivmecillinam 200 mg TID for 3 to 7 days to ibuprofen (Vik et al. 2018), and a multi-center, randomized, double-blinded study that compared pivmecillinam to cephalexin (Menday 2000). These studies were reanalyzed per

FDA's guidance for industry *Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment* ([August 2019](#)) and are included in the evaluation of benefit (Section [6](#)).

The proposed dosage regimen was supported by nonclinical pharmacokinetic (PK)/pharmacodynamic (PD) index and the dose response in the clinical studies.

The safety review focused primarily on randomized studies in adults with uUTI that were either placebo- or active comparator-controlled, evaluating a pivmecillinam dose of 200 mg TID including Ferry 2007, Bresky 1977, and Munday 2000 with supportive data from Nicolle 2002.

3.1. Review Issue List

The following review issues were identified and discussed in Section [6.3](#) Key Efficacy Review Issues and Section [7.6](#) Safety Results:

3.1.1. Key Efficacy Review Issues

3.1.1.1. Efficacy in Relation to Other Antimicrobial Comparators

One primary and one supportive efficacy study failed to demonstrate noninferiority to the comparators; see Section [6.3.1](#).

3.1.1.2. Longer-Term Efficacy Data for Two Primary Efficacy Studies

The timing of assessment for key secondary endpoints performed after 3 to 7 days of treatment resulted in a lack of longer-term data for two of the three primary efficacy studies (Munday and Vik); see Section [6.3.2](#).

3.1.1.3. Efficacy Against Pathogens Other Than *E. coli*, Including Producers of ESBLs

Sample sizes in pathogen subgroups other than *E. coli* were too small to evaluate differences between outcomes in these subgroups. Data on ESBLs were not collected in the efficacy studies; see Section [6.3.3](#).

3.1.2. Key Safety Review Issues

3.1.2.1. Carnitine Deficiency

Clinical studies of pivalate-conjugated antibacterials have demonstrated an increased risk of secondary carnitine deficiency related to the pivoxil moiety; see Section [7.7.1](#).

3.1.2.2. Porphyria

During postmarketing experience outside the U.S., rare reports of porphyria have been associated with use of pivmecillinam; see Section [7.7.2](#).

3.2. Approach to the Clinical Review

This NDA contained published manuscripts, available clinical study reports, legacy datasets and an Applicant reanalysis of efficacy and safety studies for pivmecillinam for the treatment of uUTI in adult females. Three efficacy studies were considered primary as they evaluated the recommended dosage regimen of 200 mg TID for 3 to 7 days: one placebo-controlled study ([Ferry et al. 2007](#)) and two comparative studies ([Menday 2000](#); [Vik et al. 2018](#)). The application included three supportive efficacy studies that evaluated other dosing regimens or did not include detailed clinical assessments. The efficacy review will focus on Ferry 2007, Menday 2000, and Vik 2018 as primary efficacy studies ([Menday 2000](#); [Nicolle et al. 2002](#); [Ferry et al. 2007](#); [Vik et al. 2018](#)).

The application included safety analyses from 11 studies, but focused on the 3 randomized, controlled studies that evaluated pivmecillinam in adults with uUTI with a dose of 200 mg TID, and 1 supportive randomized, controlled study evaluating a dose of 200 mg BID ([Nicolle et al. 2002](#)). As the dose, regimen, duration of therapy, and comparator differed among the different studies, studies were not pooled for safety analyses.

Additional data to support the safety assessment included postmarketing data from the periodic safety update report (PSUR) summary for MEC/pivmecillinam from Karo Pharma AB, the marketing authorization holder outside the U.S., dated September 4, 2023, covering the period of July 1, 2022, to June 30, 2023, a comprehensive review of the medical literature, and a meta-analysis of randomized clinical studies comparing the safety and efficacy of different pivmecillinam regimens for uUTI ([Pinart et al. 2017](#)). The Applicant also provided outcome data on pregnancy, lactation, and reproductive potential from the safety database acquired from Leo Pharma on February 28, 2021, and data from the public European Medicines Agency safety database and aggregate (PSUR) data from Karo Pharma AB, from February 28, 2021, until the NDA submission.

[Table 3](#) provides an overview of clinical studies important to the review of pivmecillinam's safety and efficacy. The review team identified key benefit and risk issues at the pre-NDA and early NDA review meetings. The key benefit and risk issues are addressed in Section [6.3](#) Key Efficacy Review Issues and Section [7.6](#) Safety Results, respectively. Several information requests were sent to the Applicant to supplement or clarify information in the NDA.

Table 3. Primary Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations^a for Pivmecillinam

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ^b	Number of Centers and Countries
Ferry 2007 (MET9401)	Females ≥17 years with uUTI and symptom score of ≥2 (17 to 88 y)	DR, PC, PG, R, DB Efficacy (primary) Safety (primary) Control type: placebo concurrent Randomization ratio 1:1:1:1 Double-blind	<u>Drug:</u> PIV <u>Dosage:</u> 200 mg TID; 200 mg BID; 400 mg BID, and placebo <u>Number treated:</u> • N=294, 200 mg BID x 7 d • N=282, 200 mg TID x 7 d • N=287, 400 mg x 3 d • N=291, placebo TID x 3 d <u>Duration (quantity and units):</u> 7 d	<u>Primary:</u> proportion of subjects who were both bacteriologically and clinically cured at test-of-cure visit (Days 8 to 10) <u>Key Secondary:</u> 1) Microbiological Response (bacteriologically cured) 2) Clinical Response (clinically cured)	<u>Planned:</u> 1200 (300 per treatment group) <u>Actual:</u> 1162 total randomized (287, 295, 289, 291)	<u>Centers:</u> 18 <u>Countries:</u> 1 (Sweden)
Menday 2000 (Study 2641)	Females and males 18 to 87y with uUTI	AC, PG, R, DB, noninferiority Efficacy (primary) Safety (primary) Control Type: Active concurrent, noninferiority Randomization ratio 1:1 <u>Blinding:</u> Double-blind	<u>Drug:</u> PIV <u>Dosage:</u> 200 mg TID <u>Number treated:</u> 219 (213 females) <u>Duration:</u> 3 d	<u>Primary:</u> proportion of subjects who were both bacteriologically and clinically cured (Day 10±2) <u>Key Secondary:</u> 1) Microbiological Response 2) Clinical Response 3) Safety: • Frequency of AEs compared between treatment groups	<u>Planned:</u> 640 (Approx. 20 subjects per study center) <u>Actual:</u> 441 (219; 213 females PIV)	<u>Centers:</u> 28 (per publication) <u>Countries:</u> 1 (USA)

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ^b	Number of Centers and Countries
Vik 2018	Adult females with uUTI (18 to 60 y)	AC, PG, R, DB, noninferiority Efficacy only (primary)	Drug: PIV Dosage: 200 mg TID Number treated: 189 Duration: 3 d	<u>Primary:</u> proportion of subjects who were both bacteriologically and clinically cured (Day 14) <u>Key Secondary:</u> 1) Microbiological Response 2) Clinical Response	<u>Planned:</u> 400 <u>Actual:</u> 383 (189 PIV, 194 ibuprofen)	<u>Centers:</u> 16 <u>Countries:</u> 3 (Norway, Denmark, Sweden)
Nicolle 2002 (MET 9803)	Adult females with uUTI (17 to 84 y)	AC, PG, R, DB Efficacy (supportive) Safety (primary) Randomization Ratio: 1:1 <u>Blinding:</u> Double-blind	<u>Drug:</u> PIV <u>Dosage:</u> 400 mg BID PIV and norfloxacin <u>Number treated:</u> 479 PIV, 467 norfloxacin <u>Duration:</u> 3 d	<u>Primary:</u> Proportion of subjects with a positive urine culture at baseline who were bacteriologically cured at Day 11 <u>Secondary:</u> <u>Efficacy:</u> - Proportion of subjects with a clinical cure at each follow-up visit and bacteriological outcome at the Day 39 visit <u>Safety:</u> - Frequency of adverse events compared between treatment groups (Day 4, 11, and 39)	<u>Planned:</u> 840 (420 per treatment group) <u>Actual:</u> 946 randomized (467 PIV and 479 norfloxacin, 946 total in the safety population)	<u>Centers:</u> 83 <u>Countries:</u> 9 (Austria, Belgium, Canada, Denmark, France, Ireland, Netherlands, Switzerland, UK)

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ^b	Number of Centers and Countries
Bresky 1977	Adult outpatients with uUTI (16 to 75 y)	AC, PG, R (Part 1 only), OL Efficacy (supportive) Safety (primary) <u>Control Type:</u> • Part 1: Active concurrent (amoxicillin) • Part 2: OL single arm Randomization Ratio: 1:1:2 <u>Blinding:</u> NA	<u>Part 1:</u> <u>Drug:</u> PIV <u>Dosage:</u> Part 1: PIV 400 mg TID Part 2: PIV 200 mg TID <u>Number treated:</u> PIV Part 1: 114, 400 mg TID Part 2: 84, 200 mg TID <u>Duration:</u> 10 d	<u>Primary:</u> Safety: • Incidence of AEs (timing unknown) Efficacy: • Microbiologic cure within 10 d post-treatment <u>Secondary:</u> NA	<u>Part 1</u> <u>Planned:</u> Not provided <u>Actual:</u> 374	<u>Center:</u> 1 <u>Countries:</u> 1 (Sweden)

Source: Clinical Reviewer and CDS; adapted from M2.7.6 Synopses of Individual Studies, M5.3.5.1, Clinical Study Reports/Statistical Analysis Plans, individual study publications (Bresky 1977; Menday 2000; Nicolle et al. 2002; Ferry et al. 2007; Vik et al. 2018), and adsl.xpt

^a Includes clinical studies considered primary for evaluation of efficacy and/or safety. Supportive clinical studies for efficacy and safety are summarized in Section 15, Table 92 and 93. Table does not include phase 1 and pharmacokinetic studies.

^b If no randomization, then replace with "Actual Enrolled".

Abbreviations: AC, active-controlled; AE, adverse event; BID, twice daily; d, day; DB, double-blind; DR, dose-ranging; h, hour; LTE, long-term extension; MC, multicenter; mo, month(s); N, number of subjects; NA, not applicable; NCT, national clinical trial; OL, open-label (if blinding not specified, studies presumed to be OL); PC, placebo-controlled; PG, parallel group; PIV, pivmecillinam; R, randomized; TID, three times daily; uUTI, uncomplicated urinary tract infection; wk, week(s); y, year(s)

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Nonclinical MEC Pharmacokinetics/Pharmacodynamics Information

The Applicant conducted several studies examining the nonclinical PK/PD properties of MEC in a neutropenic thigh infection and urinary tract infection murine models with *E. coli* strains. The findings showed that the fraction of time of the dosing interval (τ) for which free drug concentrations exceed the minimum inhibitory concentration (MIC) ($\%T_{fC>MIC}/\tau$) was the PK/PD index best correlated with thigh and urine bacterial burden reduction, indicating that the antibacterial activity of MEC was time dependent, similar to other penicillins. In addition,

species specific MEC $\%T_{fC>MIC}/\tau$ targets associated with stasis and 1-log10 bacterial kill are reported in [Table 5](#).

Table 5. Summary of *E. coli* Species MICs and Murine PK/PD Targets by Infection Model Type

Infection Model Type (Number of Strains)	<i>E. Coli</i> MICs ($\mu\text{g/mL}$) Range	Target Matrix	$\%T_{fC>MIC/\tau}$ ^a Median (Range)		
			Stasis	1-log10 Kill	2-log10 Kill
Neutropenic thigh infection model (4)	0.38- 16 ^b	Plasma	25% (20.7, 50.7)	81.1% (Not achieved, 88.9)	NR
Mouse UTI model (3)	0.5-96	Urine	NR	20% (NR ^c)	50% (NR ^c)

Source: FDA Reviewer's Table from Section [14.2.1](#)

^a Plasma PK/PD target for thigh infection model, Urine PK/PD target for UTI model.

^b Including one susceptible strain producing the carbapenemase NDM-1, and one resistant ESBL producing strain.

^c Only one strain allowed curve-fitting along an entire range of exposures.

Abbreviations: MIC, minimum inhibitory concentration; NA, not achieved; NR, not reported; UTI, urinary tract infection

Based on the review of provided MEC PK/PD information (Summarized in Section [14.2.1](#)), the following concerns were identified:

- Poor *E. coli* growth in the murine UTI infection model may have led to underestimation of the $\%T_{fC>MIC}/\tau$ targets associated with the bacterial burden reduction endpoints.
- Knowledge gaps were identified in terms of utility of nonclinical urinary PK/PD information in predicting clinical activity. For example, what degree of bacterial kill is associated with clinical success.

While nonclinical data support MEC activity against urine pathogens, it remains to be established within the scientific community, how to generate robust and informative nonclinical PK/PD data from uncomplicated urinary tract infection models, as well as what considerations are important during translating nonclinical urinary PK/PD evaluations into clinical efficacy predictions. The translational utility of these nonclinical PK/PD findings remains limited at this time (See Section [14.2.1](#) for more details).

Additional Nonclinical Assessments

In vitro and in vivo activities of MEC are covered in depth in Sections [19](#) and [20](#) of the Clinical Microbiology review of this IAMA. Some of the highlights are provided below:

- In vitro MIC data of MEC and other comparator drugs were submitted against 3,303 recent Enterobacterales UTI isolates from the U.S. surveillance studies between 2018 and 2020 [*IHMA combined report (3500, 4118, 4504)*]. MIC tests were performed by agar dilution method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. Against Enterobacterales isolates, the MIC₅₀/MIC₉₀ of MEC was 0.25/4 $\mu\text{g/mL}$ with an MIC range of ≤ 0.015 to >128 $\mu\text{g/mL}$. Using the CLSI susceptible MIC cut-off of ≤ 8 $\mu\text{g/mL}$ for MEC ([CLSI 2024](#)), 94.5% to 95.3% isolates appeared to be susceptible.
- The antibacterial spectrum of activity of MEC includes susceptible gram-negative isolates of Enterobacterales species that are associated with UTIs (e.g., *Citrobacter freundii*, *Enterobacter cloacae*, *E. coli*, *K. aerogenes*, *K. oxytoca*, *K. pneumoniae*, and *P. mirabilis*).

- In vitro activities of MEC and other comparators against genetically characterized extended spectrum beta-lactamase (ESBL) and carbapenemase-producing Enterobacterales clinical isolates have been reported in various studies. Susceptibility and resistance were evaluated using the CLSI or the European Committee on Antimicrobial Susceptibility Testing published interpretive criteria. Overall, MEC was reported to be active against CTX-M- (variants included 1, 14, 15, 27), AmpC-, TEM-1-, OXA-1-, NDM-1-, OXA-48-like-, IMI-, IMP-producing *E. coli* and some *K. pneumoniae* isolates. Most *E. coli* isolates were susceptible to MEC compared to *K. pneumoniae*.
- No in vitro MIC data of MEC against baseline isolates were provided from any of the efficacy studies in the NDA submission. The Applicant categorized baseline isolates as susceptible, intermediate, or resistant based on disk diffusion breakpoints and then assigned MIC values to the isolates using the CLSI mecillinam MIC breakpoints, i.e., susceptible (S) ≤ 8 $\mu\text{g/mL}$, intermediate (I) 16 $\mu\text{g/mL}$, and resistant ≥ 32 $\mu\text{g/mL}$.
- No cross-resistance has been reported between MEC and other β -lactam classes of antibacterials. The mechanism of action of MEC is inhibition of PBP-2 as compared to other β -lactams that target peptidoglycan synthesis for cell-wall inhibition by binding to PBP-3 and PBP-1.
- The frequencies of in vitro resistance mutations to MEC observed in *E. coli* varied from 8×10^{-8} to 2×10^{-5} per cell when exposed to 32-256 times MIC ([Thulin et al. 2015](#)). Though mutants were generated in vitro, many of these mutants showed large reductions in fitness, suggesting that despite the high frequency of mutation to resistance in vitro, resistance development remains low in clinical settings because most of these mutants grow too slowly to be stably maintained. Among all the mutant types found in vitro, only a small subset was fit enough to be stably maintained in the bladder.
- In vivo activities of MEC were demonstrated in mouse models of neutropenic thigh infection, UTI, and meningitis against infections caused by *E. coli*.

5.2. Clinical Pharmacology / Pharmacokinetics

Pivmecillinam (PIV) is a prodrug that is postulated to be rapidly and completely converted to MEC (the active antibacterial moiety) in the body by nonspecific esterases. A summary of MEC clinical pharmacology and pharmacokinetics is listed in [Table 6](#), unless indicated otherwise.

Table 6. Summary of MEC Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	PIV is a penicillin class antibacterial.
Mechanism of action	MEC binds to penicillin binding protein 2 (PBP-2) inhibiting biosynthesis of the bacterial cell wall.
Active moieties	MEC
QT prolongation	A thorough QTc assessment or exposure-QT prolongation relationship assessment was not conducted for MEC as part of the current application. Nonetheless, QTc prolongation is not described or identified as a risk from MEC's long term use.

Characteristic	Drug Information						
	General Information						
Bioanalysis	Validated HPLC method was used to determine MEC concentrations in human serum, plasma, and/or urine. A bioassay was also used for MEC PK assessments. Due to the lack of assay performance information for the bioassay for all clinical pharmacology studies, only qualitative inferences are included in this review, except from one study (Patel et al. 1985) that provided supportive method performance information. See Section 14.3 Bioanalytical Method Validation and Performance.						
Healthy subjects versus patients	The Applicant has not provided information on the influence of uncomplicated UTI disease on MEC PK following oral PIV administration.						
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Table 7. Steady State Plasma MEC PK Parameters in Healthy Females <table> <tr> <th>Parameter</th><th>Mean±SD</th></tr> <tr> <td>AUC</td><td>214±44 µg•min/mL</td></tr> <tr> <td>C_{max}</td><td>1.7±1.1 µg/mL</td></tr> </table> Source: (Heikkilä et al. 1992) (See also Section 14.2.3) Note: Dose: 200 mg PIV HCL Abbreviations: AUC, area under the concentration time; C_{max}, maximum plasma concentration; PK, pharmacokinetic	Parameter	Mean±SD	AUC	214±44 µg•min/mL	C _{max}	1.7±1.1 µg/mL
Parameter	Mean±SD						
AUC	214±44 µg•min/mL						
C _{max}	1.7±1.1 µg/mL						
Range of effective dose(s) or exposure	No clinical exposure-response evaluations were performed as part of the current application (See Section 6 Efficacy [Evaluation of Benefit] and Section 16 Efficacy).						
Maximally tolerated dose (MTD) or exposure	A MTD has not been determined. For oral PIV, the highest evaluated single dose in humans was 800 mg and the highest evaluated multiple doses in humans were either 600 mg BID for 6 days (1,200 mg total daily dose) or 400 mg four times daily (QID) for 4 to 8 days (1,600 mg total daily dose). For IV MEC, the highest evaluated single dose in humans was 1,000 mg MEC and the highest evaluated multiple doses in humans were 400 mg MEC four times daily for 5 days (See Section 7 Safety [Risk and Risk Management] and Section 14 Clinical Pharmacology).						
Dose proportionality	Over the dose range of 200 mg to 800 mg PIV HCL, MEC AUC increased in an approximately dose proportional manner and C _{max} increased in a less than dose proportional manner (approximately 50%).						
Accumulation	No significant MEC accumulation following the proposed three times a day oral PIV dosing is expected in the general adult population. In adults with creatinine clearance (CrCl) <30 mL/min accumulation ratio (C _{max, Day 7} / C _{max, Day 1}) was 1.89 (See Section 14.2.1).						
Time to achieve steady-state	Steady-state is achieved after the first dose (Day 1).						
Bridge between to-be-marketed and clinical trial/study formulations	(b) (4)						
	Absorption						
Bioavailability	25-35% of MEC following oral PIV administration. Bioavailability estimate based on comparison of dose normalized mecillinam exposure after 185 mg oral pivmecillinam administration and 200 mg IV mecillinam.						
T _{max}	MEC: 90±33 min (mean±SD)						

Characteristic	Drug Information																								
Food effect (fed/fasted)	No clinically significant food effect on MEC exposures observed.																								
Geometric least square mean and 90% CI	<table><tr><th colspan="4">Table 8. The Ratio of MEC PK Parameters (Fed State/Fasted) Following Administration of PIV Tablets</th></tr><tr><th></th><th>AUC_{0-10h}</th><th>C_{max}</th><th>T_{max}</th></tr><tr><th>Fed State</th><th colspan="2">Geometric Mean Ratio (90% CI)</th><th>Hr</th></tr><tr><td>1 hr before fed</td><td>0.95 (0.85, 1.07)</td><td>0.89 (0.80, 0.99)</td><td>T_{max} slightly delayed [1.4 vs. 1.2 (fasted)]</td></tr><tr><td>Fed</td><td>1.24 (1.12, 1.38)</td><td>1.20 (1.03, 1.40)</td><td>T_{max} slightly delayed [1.3 vs. 1.2(fasted)]</td></tr><tr><td>1 hr after fed</td><td>1.21 (1.08, 1.37)</td><td>1.14 (0.96, 1.36)</td><td>T_{max} slightly delayed [1.7 vs. 1.2 (fasted)]</td></tr></table> Source: Bornemann 1985, N2756A study report Note: Fed state = 30 minutes from completion of low-fat, high-calorie breakfast Abbreviations: AUC, area under the curve; CI, confidence interval; C_{max}, peak serum concentration; hr, hour; PIV, pivmecillinam; PK, pharmacokinetics; T_{max}, time to maximum plasma concentration.	Table 8. The Ratio of MEC PK Parameters (Fed State/Fasted) Following Administration of PIV Tablets					AUC _{0-10h}	C _{max}	T _{max}	Fed State	Geometric Mean Ratio (90% CI)		Hr	1 hr before fed	0.95 (0.85, 1.07)	0.89 (0.80, 0.99)	T _{max} slightly delayed [1.4 vs. 1.2 (fasted)]	Fed	1.24 (1.12, 1.38)	1.20 (1.03, 1.40)	T _{max} slightly delayed [1.3 vs. 1.2(fasted)]	1 hr after fed	1.21 (1.08, 1.37)	1.14 (0.96, 1.36)	T _{max} slightly delayed [1.7 vs. 1.2 (fasted)]
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1 hr after fed	1.21 (1.08, 1.37)	1.14 (0.96, 1.36)	T _{max} slightly delayed [1.7 vs. 1.2 (fasted)]																						
Distribution																									
Volume of distribution	MEC: 49±20 L (mean±SD)																								
Plasma protein binding	MEC: <25%																								
Drug as substrate of transporters	MEC is a substrate of MATE1, MATE2-K, and OAT3 drug transporters																								
Elimination																									
Mass balance results	A dedicated human radiolabeled mass balance study was not performed for PIV. PIV is converted to MEC, which is primarily excreted in urine. No circulatory PIV is identified.																								
Clearance	MEC: 580±100 mL/min (mean±SD)																								
Half-life	MEC: 61±32 min (mean±SD)																								
Metabolic pathway(s)	PIV is converted to MEC in vivo by nonspecific esterases. MEC is likely not a clinically relevant CYP enzymes substrate.																								
Primary excretion pathways (% dose)	Urinary excretion, primarily as MEC (approximately 80%*).																								
Intrinsic Factors and Specific Populations																									
Body weight	Not evaluated. See also Section 14.5 Pharmacometrics Assessment																								
Age	Not evaluated. See also Section 14.5 Pharmacometrics Assessment																								
Renal impairment	No dosage adjustments are recommended based on renal function. Reductions in systemic elimination as well as urinary excretion of MEC are anticipated with decreases in renal function. The clinical significance of these changes on efficacy is unknown. The available safety information does not suggest a need for dosage adjustment. See also Section 7 Safety (Risk and Risk Management), Section 8 Therapeutic Individualization, and Section 14.2.1 Mouse Pharmacokinetics and Pharmacodynamics.																								
Hepatic impairment	The effect of hepatic impairment on the pharmacokinetics of PIV or MEC was not evaluated. However, hepatic impairment is not expected to significantly alter the elimination of MEC as it is primarily renally eliminated. No dosage adjustment is recommended.																								

Characteristic	Drug Information
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	MEC: No or low inhibition and induction potentials based on in vitro DDI results
Inhibition/induction of transporter systems	MEC: No or low inhibition potentials based on in vitro DDI results
	Immunogenicity (if Applicable)
Bioanalysis	NA
Incidence	NA
Clinical impact	NA

Source: Section 14, Reviewer compiled information from NDA submission or Reviewer's independent assessment.

* Excretion estimate based on PK data following intravenous administration of mecillinam

Abbreviations: AUC, area under the curve; BID, twice daily; CI, confidence interval; Cmax, peak serum concentration; EPC, established pharmacologic class; HPLC, high-performance liquid chromatography; IV, intravenous; MEC, mecillinam; MTD, maximally tolerated dose; NA, not applicable; PBP-2, penicillin binding protein 2; PIV, pivmecillinam; PK, pharmacokinetics; QID, four times daily; SD, standard deviation; TID, three times daily; UTI, urinary tract infection

5.3. Clinical Microbiology-Mechanism of Action

Pivmecillinam hydrochloride is a prodrug of MEC. It is a penicillin class antibacterial drug. Like other β -lactam antibacterials, MEC is bactericidal and interferes with the biosynthesis of the bacterial cell wall. While penicillin and cephalosporins bind preferentially to PBP-1 and PBP-3, the target for MEC is different. It binds exclusively to the PBP-2 of gram-negative bacteria, specifically Enterobacterales ([Spratt 1977](#)). Following binding to PBP-2, bacteria lose the rod-shaped structure, and forming large, spherical cells leading to cell lysis and cell death.

The PBP-binding of MEC was investigated in membrane fractions from two *K. pneumoniae* strains, ATCC43816 and ATCC13883 ([Sutaria et al. 2018](#)). The IC₅₀ data demonstrated that MEC exhibited highly preferential binding to PBP-2 in both strains ([Table 9](#)).

Table 9. Inhibitory Activity (IC₅₀) of MEC on PBPs From Two *K. pneumoniae* Strains in mg/L

	MIC	PBP-1a/b	PBP-2	PBP-3	PBP-4	PBP-5/6
ATCC 43816	0.125	>256	<0.0075	128	>256	>256
ATCC 13883	>32	>256	<0.0075	>256	128	>256

Source: Table 1 in ([Sutaria et al. 2018](#))

Abbreviations: IC₅₀, half maximal inhibitory concentration; MEC, mecillinam; MIC, minimum inhibitory concentration; PBP, penicillin binding protein

The precise mechanism of action for MEC against *S. saprophyticus* is unknown and has not been elucidated in any studies. However, MEC achieved overall success that was better than the placebo or comparator drugs against uUTIs caused by *S. saprophyticus* in the primary efficacy studies. Several studies have also been reported that MEC demonstrated higher clinical efficacy in uUTI caused by *S. saprophyticus* isolates. In these studies, clinical isolates of *S. saprophyticus* were eradicated with MEC MIC values ranging from 8 to 64 mg/L ([Nicolle 2000](#); [Jansaker et al. 2018](#)). Therefore, at high urine concentrations of MEC (>200 mg/L) with the recommended dosing regimen, *S. saprophyticus* are unable to thrive. At concentrations approaching the MIC, antibacterials behave like toxins against susceptible bacteria ([Bernier and Surette 2013](#)).

Alternatively, it is hypothesized that higher intracellular concentration of MEC results in a form of allosteric interaction with *S. saprophyticus* PBPs. Binding of MEC at a site other than the enzyme's active site may result in a conformational change and/or a change in protein dynamics that may allow MEC at higher intracellular concentrations to interfere with bacterial growth.

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The Applicant's proposed pivmecillinam HCL (PIV) dosage (200 mg TID for 3 to 7 days) was evaluated in three primary efficacy studies: Ferry 2007, Munday 2000, and Vik 2018 ([Munday 2000](#); [Ferry et al. 2007](#); [Vik et al. 2018](#)). Supportive dose-response evidence is provided from Ferry 2007 and two additional supportive studies: Bresky 1977 and Hansen 1981 ([Bresky 1977](#); [Hansen et al. 1981](#); [Ferry et al. 2007](#)).

Primary Efficacy Studies (Ferry 2007 Study, Munday 2000 Study, and Vik 2018 Study)

The following summary results from three primary efficacy studies (See Section [6.2](#) Clinical Studies Intended to Demonstrate Efficacy for details) provide the evidence for effectiveness:

- Ferry 2007 Study: Approximately 60% of the subjects in the two 200 mg PIV treatment arms (200 mg PIV TID or BID for 7 days) and 46% of the subjects in the 400 mg PIV BID for 3 days arm were overall responders compared to only 10% responders in placebo arm ([Ferry et al. 2007](#)).
- Vik 2018 Study: Approximately 66% of the subjects in the 200 mg PIV treatment arm (200 mg TID for 3 days) were responders compared to 22% of the subjects in the ibuprofen arm (600 mg TID for 3 days) were overall responders ([Vik et al. 2018](#)).
- Munday 2000 Study: Approximately 72% of the subjects in the 200 mg PIV treatment arm (200 mg TID for 3 days) were responders compared to 76% of the subjects in the cephalexin arm (200 mg for 7 days) were overall responders. Note: the PIV treatment arm failed to demonstrate noninferiority in efficacy in relation to the comparator cephalexin. This issue is discussed further as Key Review Issue 1. For additional details see Section [6.3.1](#) ([Munday 2000](#)).

Dose-Response Studies (Ferry 2007 Study, Bresky 1977 Study, and Hansen 1981 Study)

Regardless of dosing frequency, similar microbiological success rates were observed with 400 mg PIV doses compared to 200 mg PIV doses ([Table 10](#)). These findings support the Applicant proposed PIV dosage of 200 mg TID. For additional details see Section [16](#).

Table 10. Summary of Pivmecillinam Dose-Response Information

Study	Microbiological Success Rates (Treatment Duration) ^a			
	200 mg BID	200 mg TID	400 mg BID	400 mg TID
Bresky et al. 1977		89% (x10 days)	90% (x10 days)	
Ferry et al. 2007	94% (x7 days)	93% (x7 days)	84% (x3 days)	
Hansen et al. 1981		87% (x7 days)		93% (x3 days)

Source: (Bresky 1977; Hansen et al. 1981; Ferry et al. 2007)

^a Percentages reported are the original publication values and not reanalysis values as two of three 400 mg results were not recalculated in the report.

Abbreviations: BID, twice daily; TID, three times daily

Additional Clinical Pharmacology Information

The Applicant also provided nonclinical PK/PD information, population PK modeling analyses, and urinary probability of target attainment results in support of the proposed PIV dosage. However, due to significant limitations with the provided PK data and current knowledge gaps with respect to the association between urinary probability of target attainment outcomes and clinical response rate, this additional clinical pharmacology information was deemed inadequate to support the proposed PIV dosage selection or susceptibility test interpretive criteria (See Section 5.1 Nonclinical Assessment of Potential Effectiveness, Section 14.2.1, and Section 14.5 Pharmacometrics Assessment for additional details). Nevertheless, the provided nonclinical PK/PD information does show that like other penicillins, for MEC, the fraction of time of the dosing interval (τ) for which free drug concentrations exceed the MIC ($\%fT_{C>MIC}/\tau$) was the PK/PD index correlating with its antibacterial activity. These findings support the Applicant proposed more frequent TID dosing regimen (b) (4).

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

Utility met with the FDA on October 31, 2018, July 11, 2019, and April 6, 2021, to discuss the use of PIV for the treatment of uUTI. FDA provided recommendations for the reanalysis of efficacy studies to align with the uUTI guidance document (August 2019). Analysis populations are described in Section 6.2 Clinical Studies/Trials Intended to Demonstrate Efficacy and inclusion/exclusion criteria, analysis methods and results are summarized for each study. Refer to Section 16 Efficacy for discussion of the designs and analyses according to the original protocols, which were generally consistent with the reanalysis results.

Of the six studies reanalyzed in the ISE, three were considered primary because they included the recommended dosage regimen of 200 mg TID for 3 to 7 days:

- One placebo-controlled study (Ferry et al. 2007)
- Two comparative studies (Menday 2000; Vik et al. 2018)

The remaining three studies were considered supportive because they evaluated other dosing regimens or did not include detailed clinical assessments:

- Two comparative studies (Bresky 1977; Nicolle et al. 2002)
- One study evaluating only two regimens of PIV (Hansen et al. 1981)
- See Table 3 for a summary of the primary efficacy studies.

Demographics and Baseline Characteristics of the Primary Clinical Studies in Support of Efficacy

Demographic characteristics for the three primary efficacy studies are shown in [Table 11](#) for the micro-ITT analysis set. For the Ferry study, data on the PIV 200 mg TID x 7 days regimen is provided. The mean age in the Ferry study (PIV 200 mg TID x 7 days arm and placebo arm) was 45 years and approximately 30 years in both arms in the Menday and Vik studies. In the Ferry study 23% and 16% of subjects were over age 65 in the PIV 200 mg TID for 7 days arm and placebo arm, respectively. Approximately 10% of subjects in both study arms were older than 65 years in the Menday study. The Vik study did not have subjects over the age of 65 years. Reanalysis of the primary studies contained only data for adult females.

Table 11. Demographic Characteristics: Primary Efficacy Studies, Micro-ITT Analysis Set

Characteristics	Menday 2000		Vik 2018		Ferry 2007	
	Pivmecillinam 200 mg TID × 3 Days N=127	Cephalexin 250 mg QID × 7 Days N=132	Pivmecillinam 200 mg TID × 3 Days N=105	Ibuprofen 600 mg TID × 3 Days N=119	Pivmecillinam 200 mg TID × 7 Days N=137	Placebo N=134
Age (years), n	127	132	105	119	137	134
Mean (SD)	31.8 (17.38)	31.2 (17.17)	28.9 (11.01)	28.7 (9.35)	44.6 (19.06)	45.2 (17.71)
Median	25	23.5	25	25	42	44
Min, max	18, 85	18, 87	18, 59	18, 58	18, 82	18, 83
≤24 years, n (%)	62 (48.8)	75 (56.8)	49 (46.7)	55 (46.2)	26 (19)	23 (17.2)
25 to <50 years, n (%)	47 (37)	38 (28.8)	46 (43.8)	57 (47.9)	57 (41.6)	57 (42.5)
≥50 years, n (%)	18 (14.2)	19 (14.4)	10 (9.5)	7 (5.9)	54 (39.4)	54 (40.3)
≤65 years, n (%)	112 (88.2)	120 (90.9)	105 (100)	119 (100)	106 (77.4)	113 (84.3)
>65 years, n (%)	15 (11.8)	12 (9.1)	0 (0)	0 (0)	31 (22.6)	21 (15.7)

Source: Table 14 of the ISE; ([Menday 2000](#); [Ferry et al. 2007](#); [Vik et al. 2018](#))

Note: Percentages are calculated as n/N x 100

Abbreviations: ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in the micro-intent-to-treat (micro-ITT) analysis set; n, number of subjects in the specified category; QID, four times daily; SD, standard deviation; TID, three times daily

At baseline, the majority of subjects in both arms of the Ferry study had moderate urinary frequency, while the majority of subjects in each arm of the Menday and Vik studies had moderate-severe urinary frequency. The majority of subjects in the Menday and Vik studies had severe urinary urgency (results were missing for all subjects in the Ferry study). The majority of subjects in both arms of the Ferry study had moderate dysuria, while the majority of subjects in both arms of the Menday study had severe dysuria. The majority of subjects in the PIV arm of the Vik study had moderate dysuria while an equal percentage of subjects in the ibuprofen arm of the Vik study had moderate and severe dysuria. Suprapubic pain was absent in 45% of the subjects in both arms of the Ferry study and in 100% of the subjects in the Menday study (results were missing for all subjects in the Vik study). See [Table 12](#) for details.

Table 12. Clinical Signs and Symptoms at Baseline: Primary Efficacy Studies, Micro-ITT Analysis Set

Categories	Menday 2000		Vik 2018		Ferry 2007	
	Pivmecillinam 200 mg TID × 3 Days N=127, n (%)	Cephalexin 250 mg QID × 7 Days N=132, n (%)	Pivmecillinam 200 mg TID × 3 Days N=105, n (%)	Ibuprofen 600 mg TID × 3 Days N=119, n (%)	Pivmecillinam 200 mg TID × 7 Days N=137, n (%)	Placebo N=134, n (%)
Urinary frequency, N ₁	121	126	94	96	137	134
Absent	4 (3.3)	1 (0.8)	2 (2.1)	0 (0)	2 (1.5)	6 (4.5)
Mild	16 (13.2)	15 (11.9)	5 (5.3)	9 (9.4)	26 (19)	14 (10.4)
Moderate	48 (39.7)	59 (46.8)	47 (50)	42 (43.8)	67 (48.9)	67 (50)
Severe	53 (43.8)	51 (40.5)	40 (42.6)	45 (46.9)	42 (30.7)	47 (35.1)
Urinary urgency, N ₁	120	126	94	96	N/A	N/A
Absent	7 (5.8)	5 (4)	1 (1.1)	0 (0)	–	–
Mild	22 (18.3)	20 (15.9)	5 (5.3)	7 (7.3)	–	–
Moderate	43 (35.8)	43 (34.1)	36 (38.3)	36 (37.5)	–	–
Severe	48 (40)	58 (46)	52 (55.3)	53 (55.2)	–	–
Dysuria, N ₁	121	126	94	96	137	134
Absent	1 (0.8)	8 (6.3)	3 (3.2)	3 (3.1)	2 (1.5)	7 (5.2)
Mild	20 (16.5)	15 (11.9)	3 (3.2)	11 (11.5)	23 (16.8)	25 (18.7)
Moderate	41 (33.9)	47 (37.3)	52 (55.3)	41 (42.7)	67 (48.9)	61 (45.5)
Severe	59 (48.8)	56 (44.4)	36 (38.3)	41 (42.7)	45 (32.8)	41 (30.6)
Suprapubic pain ¹ , N ₁	87	85	N/A	N/A	137	134
Absent	87 (100)	85 (100)	–	–	61 (44.5)	60 (44.8)
Mild	0 (0)	0 (0)	–	–	36 (26.3)	43 (32.1)
Moderate	0 (0)	0 (0)	–	–	37 (27)	26 (19.4)
Severe	0 (0)	0 (0)	–	–	3 (2.2)	5 (3.7)

Source: Table 15 of the ISE; (Menday 2000; Ferry et al. 2007; Vik et al. 2018)

¹ In the Menday study, suprapubic pain was not assessed separately, but was listed under symptom (other) if present.

Percentages are calculated as n/N₁ × 100

Abbreviations: ITT, intent-to-treat; N, number of subjects in the micro intent-to-treat (micro-ITT) analysis set; N₁, number of subjects with the specified sign or symptom assessed at baseline; n, number of subjects in the specified category; N/A, not applicable; QID, four times daily; TID, three times daily

The vast majority of subjects in the three primary studies had *E. coli* at baseline. Among other gram-negative bacteria the next most prevalent baseline pathogen was *P. mirabilis*, which occurred almost entirely in the Menday study. *S. saprophyticus* was the most prevalent baseline gram-positive pathogen for subjects. See [Table 13](#) for details.

Table 13. Baseline Pathogens: Primary Efficacy Studies, Micro-ITT Analysis Set

Categories	Menday 2000		Vik 2018		Ferry 2007	
	Pivmecillinam 200 mg TID × 3 Days N=127, n (%)	Cephalexin 250 mg QID × 7 Days N=132, n (%)	Pivmecillinam 200 mg TID × 3 Days N=105, n (%)	Ibuprofen 600 mg TID × 3 Days N=119, n (%)	Pivmecillinam 200 mg TID × 7 Days N=137, n (%)	Placebo N=134, n (%)
Gram-Negative						
Enterobacteriaceae						
<i>Citrobacter koseri</i>	0 (0)	0 (0)	0 (0)	2 (1.7)	0 (0)	0 (0)
<i>Citrobacter species</i>	1 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.7)	2 (1.5)
<i>Enterobacter species</i>	1 (0.8)	1 (0.8)	3 (2.9)	2 (1.7)	2 (1.5)	5 (3.7)
<i>Escherichia coli</i>	104 (81.9)	107 (81.1)	88 (83.8)	96 (80.7)	121 (88.3)	107 (79.9)
<i>Klebsiella pneumoniae</i>	4 (3.1)	3 (2.3)	2 (1.9)	1 (0.8)	0 (0)	0 (0)
<i>Klebsiella species</i>	2 (1.6)	1 (0.8)	0 (0)	0 (0)	6 (4.4)	8 (6)
<i>Proteus mirabilis</i>	9 (7.1)	13 (9.8)	0 (0)	1 (0.8)	1 (0.7)	0 (0)
Gram-Positive						
<i>Enterococcus faecalis</i>	0 (0)	0 (0)	0 (0)	2 (1.7)	0 (0)	0 (0)
<i>Enterococcus species</i>	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.9)	6 (4.5)
<i>Staphylococcus aureus</i>	0 (0)	1 (0.8)	0 (0)	0 (0)	2 (1.5)	1 (0.7)
<i>Staphylococcus saprophyticus</i>	7 (5.5)	6 (4.5)	12 (11.4)	15 (12.6)	2 (1.5)	6 (4.5)
Monomicrobial gram-negative infection	119 (93.7)	125 (94.7)	93 (88.6)	102 (85.7)	129 (94.2)	121 (90.3)
Monomicrobial gram-positive infection	7 (5.5)	7 (5.3)	12 (11.4)	17 (14.3)	6 (4.4)	12 (9)
Polymicrobial infection	1 (0.8)	0 (0)	0 (0)	0 (0)	2 (1.5)	1 (0.7)

Source: Table 16 of the ISE; ([Menday 2000](#); [Ferry et al. 2007](#); [Vik et al. 2018](#))

Note: Percentages are calculated as n/N x 100.

Abbreviations: ITT, intent-to-treat; N, number of subjects in the microbiological intent-to-treat (micro-ITT) analysis set; n, number of subjects in the specified category; QID, four times daily; TID, three times daily

6.2.1. Ferry 2007 Study

6.2.1.1. Design, Ferry 2007 Study

The Ferry 2007 study was a multicenter, randomized, double-blind study in Sweden evaluating the efficacy of three dosage regimens of PIV tablets (200 mg TID for 7 days, 200 mg BID for 7 days, and 400 mg BID for 3 days) compared to placebo ([Ferry et al. 2007](#)). The study was undertaken to determine the optimal PIV dose and length of therapy, with 200 mg TID for 7 days considered the reference treatment and the 200 mg BID for 7 days and 400 mg BID (2 200 mg tabs) for 3 days considered alternative regimens.

The subjects received a diary to record symptoms of urgency, dysuria, suprapubic pain or loin pain. The severity of each symptom was rated as absent, light, moderate, or severe (score 0 to 3) three times per day (Days 1 to 7) and at follow-up visits at Days 8 to 10 and Days 35 to 49. Subjects received two identical tablets of study drug each morning and evening and one identical tablet of study drug at noon for 7 days. Depending on treatment assignment, the two tablets consisted of either two PIV 200 mg tablets or two placebo tablets, or one tablet of each (one PIV 200 mg tablet and one placebo tablet). Treatment was randomized in balanced blocks of 20.

Uropathogens from urine samples obtained at baseline and follow-up were quantified in colony-forming unit (CFU)/mL.

In the original analysis, for subjects with symptoms, significant bacteriuria (i.e., positive culture) was defined as $\geq 10^3$ /mL for primary pathogens, $\geq 10^4$ /mL for secondary pathogens, and $\geq 10^5$ /mL for doubtful pathogens; for subjects without symptoms, significant bacteriuria was defined as $\geq 10^5$ /mL for all species. Samples without bacteriuria or with nonsignificant bacterial counts were classified as negative cultures as were samples with mixed flora without one dominating species. Bacterial species in significant counts were recorded at inclusion and at the follow-up visits.

Clinical and microbiological assessments were conducted at the same time points within a given study at baseline, Days 8 to 10 and Days 35 to 49. Subject diary for signs and symptoms was also evaluated at Days 1 to 7.

6.2.1.2. Eligibility Criteria, Ferry 2007 Study

The following are the eligibility criteria for the reanalyses that were based on the FDA guidance document on uUTI ([August 2019](#)).

Inclusion Criteria

- Females ≥ 18 years
- Subjects with evidence of pyuria
- Subjects with ≥ 2 of the following symptoms: dysuria, urinary frequency, urinary urgency and suprapubic pain (or loin pain, abdominal pain, inguinal pain as determined appropriate by Applicant review)

Exclusion Criteria:

- Signs or symptoms of systemic illness such as fever ($>38^{\circ}\text{C}$), shaking chills or other clinical manifestations suggestive of complicated urinary tract infection (cUTI)
- Receipt of antibacterials for the uUTI in the 72 hours prior to first dose of study drug

The most common reason for exclusion was lack of evidence of pyuria, with most of the subjects excluded for this reason coming from the Ferry study.

Agency Comments: Additional specific inclusion/exclusion criteria varied across the studies but in general focused on ensuring the appropriate population of women with uUTI were enrolled, excluding pregnant women and those with various comorbidities or concomitant therapies. The data for subjects with evidence of pyuria was not provided for the Munday 2000 and Hansen 1981 studies ([Hansen et al. 1981](#); [Munday 2000](#)).

Concomitant Medications

Treatment with other antibacterial drugs effective for treating uUTI was discontinued at varying intervals prior to study entry and was not permitted during the study except in the case of rescue antibacterials. The Ferry study excluded subjects who received nonstudy antibacterial therapy for UTI within the past month.

Agency Comments: Specific nonstudy antibacterials (and other therapy) restrictions varied depending on the study as follows:

- *Munday 2000: Excluded subjects receiving antibacterials, urinary antiseptics, or urinary analgesics currently or within 1 week before start of study ([Munday 2000](#)).*
- *Vik 2018: Excluded subjects treated with antibacterials within the last 2 weeks; also excluded subjects being treated with probenecid, steroids, immunosuppressant drugs, or blood-thinning drugs. No additional NSAIDs were permitted during the study but subjects could take acetaminophen if needed for additional pain relief ([Vik et al. 2018](#)).*

6.2.1.3. Statistical Analysis Plan, Ferry 2007 Study

The following efficacy population analysis sets were defined for the reanalysis:

- The intent-to-treat (ITT) analysis set included all randomized subjects regardless of whether the subject received the study drug.
- The microbiologic intent-to-treat (micro-ITT) analysis set was the population used for primary efficacy reanalyses and consisted of all subjects in the ITT population with a positive urine culture at baseline defined at $\geq 10^5$ CFU/mL of a uropathogen and no more than two species of microorganisms, regardless of colony count, and no baseline pathogen nonsusceptible to the comparator study drug. The Ferry and Vik studies were exceptions to the nonsusceptibility criterion since the comparator drugs were a placebo in the Ferry study and ibuprofen in the Vik study.
- The expanded micro-ITT analysis set consisted of all subjects in the ITT population with a positive baseline urine culture ($\geq 10^5$ CFU/mL of a uropathogens), regardless of susceptibility, and no more than two species of microorganisms regardless of colony count.

The safety population included all subjects who received at least one dose of the drug during the study.

Efficacy outcomes of microbiological and clinical cure were mostly consistent with the FDA guidance document on uUTI ([August 2019](#)) (See [Table 10](#) for details).

Agency Comments: An evaluation of overall response, which was not included in the original analysis of the Menday and Vik studies, and which was redefined for the Ferry study was conducted. This reanalysis enhanced the comparability across studies with respect to study population and efficacy assessment criteria.

Per-pathogen microbiological response at test-of-cure (TOC) (Day 8 to Day 10) was assessed for each baseline pathogen using the definitions in [Table 14](#). Per the FDA guidance document on uUTI ([August 2019](#)), the criterion for eradication was defined as $<10^3$ CFU/mL of uropathogen. A subject was considered a microbiological success if all baseline pathogens were eradicated.

Table 14. Definition of Microbiological Response

Microbiological Response	Definition
Eradication (success)	Culture at TOC demonstrated $<10^3$ CFU/mL of baseline pathogen
Persistence (failure)	Culture at TOC (or last culture prior to TOC if no TOC visit within window) demonstrated $\geq 10^3$ CFU/mL of baseline pathogen
Indeterminate	No urine culture obtained, or culture results could not be interpreted ^a at TOC; contaminated ^b cultures are deemed an eradication since the baseline pathogen was not present and the subject is not a persistence (failure)

Source: Table 12 in the ISE

^a >2 species of microorganisms

^b ≤ 2 organisms including organisms that are not pathogens

Abbreviations: CFU, colony-forming unit; TOC, test-of-cure

Clinical response was determined based on clinical signs and symptoms at the TOC visit, using the clinical assessment closest to the microbiological assessment and within the TOC window. Clinical response was classified as success, failure, or indeterminate/missing. A subject was classified as a clinical success if all symptoms present at baseline had resolved (i.e., absence of symptoms) with no new UTI symptoms present and no antibacterial therapy other than the study drug used to treat the uUTI.

Subjects with new or persistent symptoms were considered to be clinical failures. If no clinical assessment was done within the TOC window, and the subject was not classified as a clinical failure on or before the TOC, the clinical outcome was considered to be indeterminate/missing.

Overall response at the TOC visit (Days 8 to Day 10) for each subject in the micro-ITT and expanded micro-ITT populations was classified as success, failure, or indeterminate based on clinical and microbiological response per [Table 15](#) below. Overall response was defined as a success only in subjects with both microbiological and clinical success.

Table 15. Definition of Overall Response

Clinical Response	Per Subject Microbiological Response ^a	Overall Response
Success	Success	Success
Success	Failure	Failure
Success	Indeterminate	Indeterminate

Clinical Response	Per Subject Microbiological Response ^a	Overall Response
Failure	Success	Failure
Failure	Failure	Failure
Failure	Indeterminate	Failure
Indeterminate	Success	Indeterminate
Indeterminate	Failure	Failure
Indeterminate	Indeterminate	Indeterminate

Source: Table 11 in the ISE

^a Microbiological success was defined as eradication of all pathogens for a given subject; failure was defined as persistence of ≥ 1 pathogens

Abbreviations: ISE, integrated summary of effectiveness

The reanalysis performed for this study is summarized in [Table 16](#) including an assessment of the data limitations that prevented strict adherence to the defined micro-ITT population or analysis of certain efficacy outcomes in some studies to align with the 2019 FDA Guidance on uUTI.

Reanalysis of data performed for the three supportive efficacy studies are outlined in detail in the Statistical Analysis Plan (Section [14.1](#)).

Table 16. Reanalysis of Subject-Level Data and Data Limitations

Study	Original analysis or data limitation	Action taken to align with 2019 FDA Guidance on uUTI or address limitations
Ferry 2007	Study/analysis population not consistent with 2019 FDA Guidance on uUTI	Re-defined study/analysis population
	Original overall response endpoint not consistent with 2019 FDA Guidance on uUTI	Re-analyzed data to include re-defined overall response
	Inclusion of subjects with urinary pathogens $<10^5$ CFU/mL at baseline	New micro-ITT population included only subjects with urinary pathogens $\geq 10^5$ CFU/mL
	Definition of microbiological cure not consistent with 2019 FDA Guidance on uUTI	Re-analyzed data utilizing criteria for negative urine culture of $<10^3$ CFU/mL in micro-ITT population; sensitivity analysis demonstrates the microbiological success threshold (10^3 versus 10^5) does not have significant impact on overall response results

Source: Table 10 of the ISE; (Ferry et al. 2007; August 2019)

Abbreviations: CFU, colony-forming unit; FDA, Food and Drug Administration; ITT, intent-to-treat; MIC, minimum inhibitory concentration; TOC, test-of-cure; uUTI, uncomplicated urinary tract infection; Y/N, Yes/No.

Agency Comments: One primary study (Ferry et al. 2007) and one supportive study (Nicolle et al. 2002) had longer-term follow-up visits (Days 35 to 49 in Ferry study and Day 39 $\pm$ 5 days in the Nicolle study). For these two studies, clinical, microbiological, and overall response were summarized in the ITT (clinical response) and micro-ITT analysis (microbiological response) populations for subjects with a longer-term follow-up visit occurring within the protocol-specified window. As with the Ferry study, the Nicolle study initially included subjects with $<10^5$ CFU/mL of uropathogen at baseline and was reanalyzed based on a new micro-ITT population including only subjects with $\geq 10^5$ CFU/mL of uropathogen. Sustained clinical response was defined as success at both the TOC and longer-term follow-up visit in the ITT and micro-ITT populations.

6.2.1.4. Results of Analyses, Ferry 2007 Study

Baseline concomitant drug treatment appeared comparable in the four treatment groups where approximately half of the subjects were taking concomitant medications at baseline.

Out of 1172 enrolled subjects, 1162 subjects were randomized in the Ferry 2007 study ([Ferry et al. 2007](#)). A total of 287 to 295 subjects were randomized in each treatment arm of the Ferry study with almost the same number in the safety population and 192-214 subjects remaining in the ITT population.

Agency Comments: Approximately 65 to 70% of subjects in the pivmecillinam 200 mg TID for 7 days arm and the placebo arm in the Ferry study, 95% of subjects in the Menday study and 85 to 90% of subjects in the Vik study who were randomized were included in the ITT population. For the reanalysis, subjects who were randomized were excluded from the ITT population if they were female and <18 years of age or male, had no evidence of pyuria, did not have at least two symptoms or had signs of cUTI.

Subjects who were randomized were most often not included in the ITT population for no evidence of pyuria.

Subjects in the ITT analysis set were excluded from the micro-ITT analysis set if they had no positive urine culture or if they were enrolled in the Menday study and had a pathogen that was nonsusceptible to the comparator. 67 to 71% of subjects in the Ferry study, 61 to 63% of subjects in the Menday study and 62 to 70% of subjects in the Vik study who were in the ITT population were included in the micro-ITT population. The vast majority of subjects in the ITT analysis set were excluded from the micro-ITT analysis set due to not having any positive urine cultures.

Subject Disposition

Among subjects in the Ferry study in the ITT population, 13% of subjects randomized to pivmecillinam 200 mg TID for 7 days discontinued from the study compared to 49% of placebo subjects. The majority of discontinuations were due to an unacceptable treatment effect, which was defined in Section 8.5.1.2 of the clinical study report as follows: A subject could withdraw from the study if she or the investigator considered the treatment effect to be unacceptable and the subject required alternative treatment. Section 8.5.1.3 of the clinical study report defined Medical Deterioration by stating that the investigator could withdraw the subject from the study at any time for medical reasons. See [Table 17](#) for details.

Section 3.2.2 of the statistical analysis plan and Section 8.17.2 of the clinical study report defines clinical relapses as “patients who were asymptomatic at Visit 2 but symptomatic at Visit 3 [Visit 2 was the 8- to 10-day follow-up visit, Visit 3 was the 35- to 49-day follow-up visit].” Both withdrawal reasons of relapses and unacceptable treatment effects were counted as failures. Table 12 in the ISE defined persistence (failure) as “Culture at TOC (or last culture prior to TOC if no TOC visit within window) [that] demonstrated $\geq 10^3$ CFU/mL of baseline pathogen.”

Table 17. Subject Disposition, ITT Population, Ferry 2007 Study

	Pivmecillinam 200 mg tid x 7 days (N=192)	Placebo (N=201)
Completed Study	167 (87.0)	102 (50.7)
Discontinued Study	25 (13.0)	98 (48.8)
Adverse Event	1 (0.5)	0 (0.0)
Disease Relapse	7 (3.6)	6 (3.0)
Failure to Meet Randomization Criteria	2 (1.0)	0 (0.0)
Unacceptable Treatment Effect	9 (4.7)	89 (44.3)
Lost to Follow-Up	5 (2.6)	2 (1.0)
Progressive Disease	1 (0.5)	0 (0.0)
Death	0 (0)	0 (0)
Voluntary Withdrawal	0 (0)	0 (0)
Study Completion Status Unknown	0 (0.0)	0 (0.0)
Source: adsl.xpt		

Source: Statistical Analyst and Statistics Reviewer; (Ferry et al. 2007)

Abbreviations: tid, three times daily

Compliance With Study Treatment

Compliance with study medication was 85 to 90% for each pivmecillinam treatment group and 74% for placebo. Mean number of doses missed ranged from 3.5 to 6.3 in each pivmecillinam treatment group and was 10.5 in the placebo arm while median number of doses missed was 2 in each pivmecillinam arm and 5 in the placebo arm. See [Table 18](#) and [Table 19](#) for details.

Table 18. Treatments Used, Safety Population, Ferry 2007 Study

	Pivmecillinam 200 mg TID x 7 Days N=282, n (%)	Pivmecillinam 200 mg BID x 7 Days N=294, n (%)	Pivmecillinam 400 mg BID x 7 Days N=287, n (%)	Placebo N=289, n (%)	Chi-Square Test
No	36 (12.9)	44 (15.2)	29 (10.2)	74 (26.4)	p<0.001
Yes	244 (87.1)	245 (84.8)	254 (89.8)	206 (73.6)	
Total	280 (100)	289 (100)	283 (100)	280 (100)	

Source: Table 51 of the Ferry Clinical Study Report; (Ferry et al. 2007)

Abbreviations: BID, twice daily; N, number of subjects in the safety population; n, number of subjects in group; TID, three times daily

Table 19. Number of Doses Missed, Safety Population, Ferry 2007 Study

	Pivmecillinam 200 mg TID x 7 Days N=282, n	Pivmecillinam 200 mg BID x 7 Days N=294, n	Pivmecillinam 400 mg BID x 3 Days N=287, n	Placebo N=289, n	Analysis of Variance
Mean	4.7	6.3	3.5	10.5	p=0.009
SD	7.2	7.8	3.3	9.5	
Median	2	2	2	5	
Minimum	1	1	1	1	
Maximum	32	30	13	27	
Number	22	20	16	38	

Source: Table 52 of the Ferry Clinical Study Report; (Ferry et al. 2007)

Note: Subjects not returning medication carton and subjects with discrepancies between number of returned tablets and ticked missing days are not included in the table.

Abbreviations: BID, twice daily; N, number of subjects in the safety population; n, number of subjects in group; SD, standard deviation; TID, three times daily

Primary Efficacy Analysis

The results of the primary efficacy analysis of the Ferry study comparing pivmecillinam 200 mg TID for 7 days to placebo using the micro-ITT analysis population is shown in [Table 20](#). Approximately 60% of the subjects in the two pivmecillinam 200 mg treatment arms and 46% of the subjects in the pivmecillinam 400 mg BID arm were successful overall responders compared to only 10% of placebo subjects. Note that although the 400 mg dose of pivmecillinam was higher than the other two active treatment arms, the 400 mg dose was only administered for 3 days as opposed to 7 days for the 200 mg dose regimens.

Within-study comparisons comparing duration of treatment were only available in the Ferry study where observed responses for the 7-day arm were 13 to -16% higher than those observed for the 3-day arm, suggesting that 7 days of treatment was the optimal duration compared to 3 days.

Table 20. Primary Efficacy Analysis of Overall Response, Micro-ITT Analysis Set, Ferry 2007 Study

Categories	Pivmecillinam 200 mg BID × 7 Days	Pivmecillinam 200 mg TID × 7 Days	Pivmecillinam 400 mg BID × 3 Days	Placebo
Success, n/N (%)	82/138 (59.4%)	85/137 (62%)	62/134 (46.3%)	14/134 (10.4%)
Risk difference	49%	51.6%	35.8%	
95% CI for RD	38.5%, 59.4%	41.2%, 62%	25.2%, 46.5%	
p-Value	<0.001	<0.001	<0.001	

Source: Statistical analyst and statistics reviewer; ([Ferry et al. 2007](#))

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the micro-ITT analysis set; n, number of subjects in group; RD, risk difference; TID, three times daily

Secondary Efficacy Analysis

Other secondary efficacy endpoints (Clinical Response and Microbiological Response) were also observed to have similar trends to the primary efficacy endpoint, with nominally significantly higher response rates compared to placebo. The majority of subjects who were not classified as treatment successes were categorized as treatment failures, followed by subjects classified as having indeterminate responses. See [Table 21](#) for details.

Table 21. Applicant's Reanalysis, Micro-ITT Analysis Set, Ferry 2007 Study

Endpoint	Response at TOC	Pivmecillinam 200 mg BID 7 days N=138 n (%)	Pivmecillinam 200 mg TID 7 days N=137 n (%)	Pivmecillinam 400 mg BID 3 days N=134 n (%)	Placebo N=134 n (%)
Overall Response	Success Difference 95% CI for the diff.	82 (59.4) 49.0 (38.5, 59.4)	85 (62.0) 51.6 (41.2, 62.0)	62 (46.3) 35.8 (25.2, 46.5)	14 (10.4)
	Failure	50 (36.2)	45 (32.8)	68 (50.7)	110 (82.1)
	Indeterminate	6 (4.3)	7 (5.1)	4 (3.0)	10 (7.5)
Clinical Response	Success Difference 95% CI for the diff.	87 (63.0) 39.9 (28.4, 51.4)	87 (63.5) 40.4 (28.9, 51.9)	69 (51.5) 28.4 (16.5, 40.2)	31 (23.1)
	Failure	47 (34.1)	43 (31.4)	61 (45.5)	93 (69.4)
	Indeterminate	4 (2.9)	7 (5.1)	4 (3.0)	10 (7.5)
Microbiological Response	Success Difference 95% CI for the diff.	120 (87.0) 60.8 (50.8, 70.9)	119 (86.9) 60.7 (50.7, 70.8)	100 (74.6) 48.5 (37.3, 59.7)	35 (26.1)
	Failure	10 (7.2)	8 (5.8)	26 (19.4)	86 (64.2)
	Indeterminate	8 (5.8)	10 (7.3)	8 (6.0)	13 (9.7)

Source: Table 17 in the ISE; (Ferry et al. 2007)

Note: Confidence interval is calculated using the Wald method with a continuity correction

Note: Percentages are calculated as n/N × 100.

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the micro-ITT analysis set; n, number of subjects in the specified category; TID, three times daily; TOC, test-of-cure visit

6.2.2. Menday 2000 Study

6.2.2.1. Design, Menday 2000 Study

The Menday 2000 study was a multicenter, randomized, double-blind study in the US evaluating the efficacy and safety of pivmecillinam 200 mg TID for 3 days compared to cephalexin 250 mg 4 times daily for 7 days (Menday 2000). Subjects were evaluated at baseline, Day 2 or 3, Day 10 (±2 days), and Day 14 (±2 days); at each visit, investigators monitored and recorded signs and symptoms of UTI including pyrexia, urinary frequency, burning and dysuria. A urine sample was also taken at each visit. To maintain the study blind, each subject received active and/or matching placebo tablets sufficient for four doses per day for 7 days.

A positive urine culture was defined as presence of a urinary bacterial pathogen at a colony count of $\geq 10^5$ CFU/mL.

6.2.2.2. Eligibility Criteria, Menday 2000 Study

Inclusion and exclusion criteria used for the reanalysis were similar to the Ferry study except that information about the inclusion criterion of pyuria was not provided for the Menday study. Female adults with acute uUTI (≤ 2 symptomatic episodes in the previous year and no recent history of obstructive uropathy, catheterization or other instrumentation of the urinary tract) were

included. Per the criteria for reanalysis, subjects were excluded from the efficacy population if they were younger than 18 years of age, male, did not have ≥ 2 symptoms, or had signs of cUTI.

Concomitant Medications

Treatment with other antibacterial drugs effective for treating uUTI was discontinued at varying intervals prior to study entry and was not permitted during the studies except in the case of rescue antibacterials.

6.2.2.3. Statistical Analysis Plan, Menday 2000 Study

Population definitions for the reanalysis were similar to those listed previously for the Ferry study. See [Table 22](#) for reanalysis of subject-level data and data limitations in the Menday study.

Table 22. Reanalysis of Subject-Level Data and Data Limitations

Study	Original analysis or data limitation	Action taken to align with 2019 FDA Guidance on uUTI or address limitations
Menday 2000	Study/analysis population not consistent with 2019 FDA Guidance on uUTI	Re-defined study/analysis population
	Overall response not reported	Re-analyzed data to include overall response
	Clinical response defined to include clinical improvement	Re-analyzed data based on clinical cure (absence of symptoms)
	Definition of microbiological cure not consistent with 2019 FDA Guidance on uUTI	Original study definition for negative culture ($<10^5$ CFU/mL) used; sensitivity analysis of Ferry study demonstrates the microbiological success threshold (10^3 versus 10^5) does not have significant impact on overall response results

Source: Table 10 of the ISE; ([Menday 2000](#); [August 2019](#))

Abbreviations: CFU, colony-forming unit; FDA, Food and Drug Administration; ITT, intent-to-treat; MIC, minimum inhibitory concentration; TOC, test-of-cure; Y/N, Yes/No

Section 6.9.3 of the ISE stated that two-sided 95% CI for the difference in success rates (pivmecillinam minus comparator) were calculated for the primary and key secondary efficacy endpoints using the normal approximation to the binominal with a continuity correction.

6.2.2.4. Results of Analyses, Menday 2000 Study

The mean age was slightly more than 30 years of age in both treatment arms in the Menday study while the median age was 24 years in both arms. Slightly more than half of the subjects (52%) were <25 years old in both arms, while 8 to 9% were at least 65 years old. The study was conducted in the United States, where 85% of the subjects in both arms were White, while 11 to 13% were Black. See [Table 23](#) for details.

Table 23. Baseline Demographics, Safety Population, Menday 2000 Study

Characteristic	PIVYA 200 mg TID $\times$ 3 Days N=213	Cephalexin 250 mg QID $\times$ 7 Days N=219
Sex, n (%)		
Female	213 (100)	219 (100)
Age, years		
Mean (SD)	30.5 (15.6)	31.4 (16.1)
Median (min, max)	24 (18, 85)	24 (18, 87)

Characteristic	PIVYA 200 mg TID × 3 Days N=213	Cephalexin 250 mg QID × 7 Days N=219
Age group, years, n (%)		
≤24	109 (51.2)	113 (51.6)
25 to <50	80 (37.6)	78 (35.6)
≥50	24 (11.3)	28 (12.8)
Age group ≥65, years, n (%)		
≥65	19 (8.9)	17 (7.8)
Age group ≥75, years, n (%)		
≥75	5 (2.3)	8 (3.7)
Race, n (%)		
Asian	1 (0.5)	2 (0.9)
Black	24 (11.3)	28 (12.8)
Caucasian	180 (84.5)	186 (84.9)
Chinese	1 (0.5)	0
Chinese + German	1 (0.5)	0
Hispanic	2 (0.9)	1 (0.5)
Japanese	1 (0.5)	0
Mexican American	0	1 (0.5)
Oriental	1 (0.5)	1 (0.5)
Spanish American	1 (0.5)	0
Missing	1 (0.5)	0
Ethnicity, n (%)		
Missing	213 (100)	219 (100)
Country of participation, n (%)		
United States	213 (100)	219 (100)
Is in United States, n (%)		
United States	213 (100)	219 (100)

Source: adsl.xpt and Menday.xpt, CDS Programmer; Software: R; ([Menday 2000](#))

Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; PIVYA, pivmecillinam; QID, four times daily; SD, standard deviation; TID, three times daily

A total of 441 subjects were enrolled and 441 subjects were randomized, with 219 subjects in the pivmecillinam arm and 222 subjects in the cephalexin arm.

Approximately 95% of the randomized subjects were included in the ITT population with 207 subjects in the pivmecillinam arm and 208 subjects in the cephalexin arm. There were 213 subjects in the pivmecillinam arm and 219 subjects in the cephalexin arm who were in the safety population.

For the Applicant's tables of Demographic Characteristics, Clinical Signs and Symptoms at Baseline, Baseline Pathogens, the Analysis Populations and Analysis Sets for the Primary Efficacy Studies as pertain to the Menday study, see Section [6.2.2](#). Note that the subject disposition table is missing because there were no data for reasons for study discontinuation in the Menday study.

The results of the primary efficacy analyses of the Menday study are shown in [Table 24](#). The percentage of subjects with overall responses in the pivmecillinam arm were somewhat lower than they were in the cephalexin arm, with the lower bound of the 95% CI of treatment differences below the noninferiority (NI) margin of -10% that was specified in the FDA guidance document on uUTI ([August 2019](#)). Hence, the NI of pivmecillinam to cephalexin was not demonstrated according to this margin.

Table 24. Primary Efficacy Analysis of Overall Response, Micro-ITT Analysis Set, Menday 2000 Study

Categories	Pivmecillinam 200 mg BID × 3 Days	Cephalexin 250 mg QID × 7 Days
Success n/N (%)	91/127 (71.7%)	100/132 (75.8%)
Risk Difference	-4.1%	
95% CI for RD	-15.6%, 7.4%	
p-Value	0.482	

Source: Statistical analyst and statistics reviewer; ([Menday 2000](#))

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified population or group; QID, four times daily; RD, risk difference

Other secondary efficacy endpoints (Clinical Response and Microbiological Response) were also observed to have similar trends to the primary efficacy endpoint, with somewhat lower response rates compared to cephalexin and lower bounds of 95% CIs below -10%. The majority of subjects who were not classified as treatment successes were categorized as treatment failures, followed by subjects classified as having indeterminate responses. See [Table 25](#) for details.

Table 25. Applicant's Reanalysis, Micro-ITT Analysis Set, Menday 2000 Study

Endpoint	Response at TOC	Pivmecillinam 200 mg TID 3 days N=127 n (%)	Cephalexin 250 mg QID 7 days N=132 n (%)
Overall Response	Success Difference 95% CI for the diff.	91 (71.7) -4.1 (-15.6, 7.4)	100 (75.8)
	Failure	29 (22.8)	24 (18.2)
	Indeterminate	7 (5.5)	8 (6.1)
Clinical Response	Success Difference 95% CI for the diff.	105 (82.7) -2.2 (-11.9, 7.6)	112 (84.8)
	Failure	20 (15.7)	12 (9.1)
	Indeterminate	2 (1.6)	8 (6.1)
Microbiological Response	Success Difference 95% CI for the diff.	97 (76.4) -3.9 (-14.7, 6.9)	106 (80.3)
	Failure	18 (14.2)	16 (12.1)
	Indeterminate	12 (9.4)	10 (7.6)

Source: Table 18 in the ISE; ([Menday 2000](#))

Note: Confidence interval is calculated using the Wald method with a continuity correction.

Note: Percentages are calculated as n/N × 100.

Abbreviations: CI, confidence interval; diff, difference; ITT, intent-to-treat; N, number of subjects in the microbiological ITT analysis set; n, number of subjects in the specified category; QID, four times daily; TID, three times daily; TOC, test-of-cure visit

6.2.3. Vik 2018 Study

6.2.3.1. Design, Vik 2018 Study

The Vik 2018 study was a multicenter, randomized, double-blind, noninferiority study to evaluate the efficacy and safety of pivmecillinam 200 mg TID for 3 days compared to ibuprofen 600 mg TID for 3 days ([Vik et al. 2018](#)). The study was conducted in Norway, Sweden, and Denmark.

Subjects used a diary to record the severity of their symptoms daily on Days 1 to 7 and to indicate on which day they felt completely cured; specifically, dysuria, urgency, frequency were graded on a scale of 0 to 6 (with 0 = “normal/not affected” and 6 = “as bad as it could be”). Subjects were contacted for a telephone follow-up after 14 and 28 days where they were asked if they felt cured (and, if so, how many days it had taken), whether they had experienced a relapse of symptoms, and if they had received antibacterial treatment.

For the Vik study, the database recorded a positive or negative urine culture at baseline and postbaseline based on the protocol-specified definition of $\geq 10^3$ CFU/mL for primary pathogens (per European guidelines at the time of the study); $\geq 10^4$ CFU/mL for secondary pathogens; and $\geq 10^5$ CFU/mL for doubtful pathogens. Since individual CFU counts were not available, the study definition of a positive or negative urine culture was assumed to have been met and the documented positive or negative result was used in the analysis. The timing of clinical and microbiological assessments was at baseline and Day 14. In addition, clinical assessments were made on Days 1 to 7 (subject diary) and Day 28 (telephone).

6.2.3.2. Eligibility Criteria, Vik 2018 Study

Inclusion and exclusion criteria were similar to the Ferry study. Women 18 to 60 years of age with clinical symptoms of uUTI (dysuria combined with increased urinary frequency and/or urgency) were included. Per the criteria for reanalysis, subjects were excluded from the efficacy population if they were younger than 18 years of age, had no evidence of pyuria, did not have ≥ 2 symptoms, or had signs of cUTI. The most common reason for exclusion was lack of evidence of pyuria.

Concomitant Medications

Treatment with other antibacterial drugs effective for treating uUTI was discontinued at varying intervals prior to study entry and was not permitted during the studies except in the case of rescue antibacterials. In this study, the need for secondary antibacterial treatment was specifically included as a secondary efficacy endpoint (i.e., indicating primary treatment failure).

6.2.3.3. Statistical Analysis Plan, Vik 2018 Study

Population definitions were similar to those listed previously for the Ferry study. The statistical analysis plan was the same as the Ferry study except exact subject-level CFU counts were not available for the Vik study and therefore this study could not be confirmed to fully adhere to the FDA guidance document on uUTI ([August 2019](#)) regarding CFU counts for inclusion of subjects in the micro-ITT analysis set and determination of microbiological outcome.

The Applicant stated “Also in the Vik study, clinical response at TOC (Day 14) was based on an overall assessment of symptomatology (“felt cured”) at Day 14 and individual symptoms graded through Day 7. For a subject to be considered a clinical success at Day 14, the subject must have had no symptoms at Day 7 (or at the last time point graded) and must have “felt cured” at Day 14.” See [Table 26](#) for details.

Table 26. Reanalysis of Subject-Level Data and Data Limitations

Study	Original analysis or data limitation	Action taken to align with 2019 FDA Guidance on uUTI or address limitations
Vik 2018	Study/analysis population not consistent with 2019 FDA Guidance on uUTI	Re-defined study/analysis population
	Overall response not reported	Re-analyzed data to include overall response
	Individual symptoms graded daily through Day 7, with a telephone contact at Day 14 to determine if the subject “felt cured”	Subject was considered a clinical cure if they were clinically cured based on individual symptoms at Day 7 (or at the last time point graded) and remain cured (“felt cured”) at Day 14
	CFU counts not included in database	The original study definition of a positive urine culture ($\geq 10^3$ CFU/mL for primary pathogens) was applied to the micro-ITT analysis based on documentation in the database confirming the subject met the protocol-specified criteria*
	Symptoms recorded on 0-6 scale	For comparability with other studies, ratings remapped to 0=none/absent, 1-2=mild, 3-4=moderate, and 5-6=severe
	MIC data not provided	Y/N variable used to indicate if pathogen susceptible to pivmecillinam
	TOC visits occurred but visit dates not provided	Assumed TOC visit occurred on Day 14
	Start and end dates (or duration) of study drug not available	Start date assumed to be the “inclusion” date

Source: Table 10 of the ISE; ([Vik et al. 2018](#); [August 2019](#))

Abbreviations: CFU, colony-forming unit; FDA, Food and Drug Administration; ITT, intent-to-treat; MIC, minimum inhibitory concentration; TOC, test-of-cure; uUTI, uncomplicated urinary tract infection; Y/N, Yes/No

A two-sided 95% CI for the difference in success rates (pivmecillinam minus comparator) was calculated using the normal approximation to the binominal with a continuity correction.

6.2.3.4. Results of Analyses, Vik 2018 Study

The mean and median ages were 28 and 25 years, respectively, in the pivmecillinam and ibuprofen treatment arms, with 6% of the subjects over 50 years in the pivmecillinam arm and 4% over 50 years in the ibuprofen arm. Almost 80% of the subjects were from Norway, followed by Denmark, and then Sweden. See [Table 27](#) for details.

Table 27. Baseline Demographics and Clinical Characteristics, Safety Population, Vik 2018 Study

Characteristics	Pivmecillinam	Ibuprofen
	200 mg TID × 3 Days	600 mg TID × 3 Days
Sex, n (%)		
Female	189 (100)	194 (100)
Age, years		
Mean (SD)	28.3 (10)	28 (8.46)
Median	25	25
Min, Max	18, 59	18, 58

Characteristics	Pivmecillinam 200 mg TID × 3 Days	Ibuprofen 600 mg TID × 3 Days
Age group, years, n (%)		
≤24 yrs	93 (49.2)	85 (43.8)
25-49 yrs	84 (44.4)	102 (52.6)
50-64 yrs	12 (6.3)	7 (3.6)
Country, n (%)		
Denmark	20 (10.6)	26 (13.4)
Norway	150 (79.4)	150 (77.3)
Sweden	19 (10.1)	18 (9.3)

Source: adsl.xpt, statistical analyst; (Vik et al. 2018)

Abbreviations: n, number of subjects in the specified category; SD, standard deviation; TID, three times daily; yrs, years

Screening data were not available for the Vik study. There were 189 subjects in the pivmecillinam arm and 194 subjects in the ibuprofen arm who were enrolled and randomized.

There were also 189 subjects in the pivmecillinam arm and 194 subjects in the ibuprofen arm who were in the Safety population. Out of these subjects, the ITT population consisted of 170 subjects in the pivmecillinam arm and 169 subjects in the ibuprofen arm.

For the Applicant's tables of Demographic Characteristics, Clinical Signs and Symptoms at Baseline, Baseline Pathogens, the Analysis Populations and Analysis Sets for the Primary Efficacy Studies as pertain to the Vik study, see Section 6.2.3. Note that the subject disposition table is missing because there were no data for reasons for study discontinuation in the Vik study.

The results of the primary efficacy analyses of the Vik study are shown in Table 28, where 66% of the subjects in the pivmecillinam arm and 22% of the subjects in the ibuprofen arm were overall responders.

Table 28. Primary Efficacy Analysis of Overall Response, Micro-ITT Analysis Set, Vik 2018 Study

Categories	Pivmecillinam 200 mg TID × 3 Days	Ibuprofen 600 mg TID × 3 Days
Success n/N (%)	69/105 (65.7%)	26/119 (21.8%)
Risk difference	43.9%	
95% CI for RD	31.2%, 56.5%	
p-Value	<0.001	

Source: Statistical analyst and statistics reviewer; (Vik et al. 2018)

Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the microbiological ITT analysis set; n, number of subjects in the specified category; RD, risk difference; TID, three times daily

Other secondary efficacy endpoints (Clinical Response and Microbiological Response) were also observed to have similar trends like the primary efficacy endpoint, with nominally significantly higher response rates compared to ibuprofen. The majority of subjects who were not classified as treatment successes were categorized as treatment failures, followed by subjects classified as having indeterminate responses. See Table 29 for details.

Table 29. Applicant's Reanalysis of Vik 2018 Study, Micro-ITT Analysis Set

Endpoint	Response at TOC	Pivmecillinam 200 mg TID 3 days N=105 n (%)	Ibuprofen 600 mg TID 3 days N=119 n (%)
Overall Response	Success Difference 95% CI for the diff.	69 (65.7) 43.9 (31.2, 56.5)	26 (21.8)
	Failure	35 (33.3)	91 (76.5)
	Indeterminate	1 (1.0)	2 (1.7)
Clinical Response	Success Difference 95% CI for the diff.	81 (77.1) 39.3 (26.6, 52.1)	45 (37.8)
	Failure	16 (15.2)	65 (54.6)
	Indeterminate	8 (7.6)	9 (7.6)
Microbiological Response	Success Difference 95% CI for the diff.	78 (74.3) 20.5 (7.4, 33.7)	64 (53.8)
	Failure	27 (25.7)	55 (46.2)
	Indeterminate	0 (0.0)	0 (0.0)

Source: Table 19 in the ISE; (Vik et al. 2018)

Note: Confidence interval is calculated using the Wald method with a continuity correction.

Note: Percentages are calculated as $n/N \times 100$

Abbreviations: CI, confidence interval; diff, difference; N, number of subjects in population; n, number of subjects in the specified category; ITT, intent-to-treat; TID, three times daily; TOC, test-of-cure visit

6.2.4. Nicolle 2002 Study

6.2.4.1. Design, Nicolle 2002 Study

Unlike the primary studies by Ferry, Menday and Vik, the Nicolle 2002 study was reviewed for supportive evidence of efficacy because the pivmecillinam 400 mg BID dosing differed from the TID dosing the Applicant is seeking for its indication (Nicolle et al. 2002). This was a multicenter, randomized, double-blind, noninferiority study evaluating the efficacy of pivmecillinam 400 mg BID for 3 days versus norfloxacin 400 mg BID for 3 days. The study was conducted in Austria, Belgium, Canada, Denmark, France, Ireland, Netherlands, Switzerland, and the United Kingdom.

Subjects were contacted by telephone on Day 4 (± 1 day) following initiation of therapy to review and record urinary symptoms; subjects were asked whether symptoms had disappeared (clinical cure), improved (clinical improvement), or were unchanged or worse (clinical failure). Subjects returned for clinical assessments and urine samples on Day 11 (± 2 days) and, if clinically cured on Day 11, again on Day 39 (± 5 days). Clinical symptoms (frequency, dysuria, urgency, and suprapubic pain) were graded as 0=absent; 1=mild; 2=moderate; or 3=severe at baseline and at each follow-up visit. Symptoms scores were recorded at the two follow-up visits only for subjects who reported symptoms on Day 4.

Urine specimens were analyzed by a central laboratory in the Netherlands using standardized methods. A positive urine culture at baseline was defined as $\geq 10^3$ CFU/mL of a uropathogen with pyuria or $\geq 10^5$ CFU/mL of a uropathogen with or without pyuria. *E. coli*, *Klebsiella spp.*, *Proteus spp.*, *S. saprophyticus*, *Enterococcus spp.*, *Pseudomonas spp.* and *Citrobacter spp.* were considered urinary pathogens. Antimicrobial susceptibility testing was done using an agar disc diffusion method.

6.2.4.2. Eligibility Criteria, Nicolle 2002 Study

Inclusion and exclusion criteria were similar to the Ferry study. Women 18 to 65 years of age with one or more symptoms of acute uUTI (frequency, urgency, dysuria, or suprapubic pain) were included. Per the criteria for reanalysis, subjects were excluded from the efficacy population if they were younger than 18 years of age, had no evidence of pyuria, did not have ≥ 2 symptoms, or had signs of cUTI.

6.2.4.3. Statistical Analysis Plan, Nicolle 2002 Study

Population definitions were similar to those listed previously for the Ferry study.

Clinical, microbiological, and overall response as defined in the Applicant's Integrated Summary of Efficacy were summarized in the ITT (clinical response) and micro-ITT analysis (microbiological response) populations for subjects with a longer-term follow-up visit occurring within the protocol-specified window. As with the Ferry study, the Nicolle study initially included subjects with $< 10^5$ CFU/mL of uropathogens at baseline and was reanalyzed based on a new micro-ITT population including only subjects with $\geq 10^5$ CFU/mL of uropathogens. Sustained clinical response was defined as success at both the TOC and longer-term follow-up visit in the ITT and micro-ITT populations.

A two-sided 95% CI for the difference in success rates (pivmecillinam minus comparator) was calculated using the normal approximation to the binomial with a continuity correction.

6.2.4.4. Results of Analyses, Nicolle 2022 Study

Screening data were not available for the Nicolle study. A total of 954 subjects were randomized out of a total of 963 who were enrolled.

Almost all of the subjects randomized to the pivmecillinam 400 mg BID and norfloxacin 400 mg BID arms were included in the Safety population, while approximately 430 subjects were included in the ITT population in both treatment arms. There were fewer subjects in the ITT population than in the Safety population because subjects in the ITT population had to meet inclusion/exclusion criteria specified for the reanalysis while subjects in the Safety population did not.

Among subjects in the Nicolle study in the ITT population, 25% of subjects randomized to pivmecillinam 400 mg BID for 3 days discontinued from the study compared to 19% of norfloxacin subjects. The majority of discontinuations were due to an unacceptable treatment effect, followed by lost to follow-up. See [Table 30](#) for details.

Table 30. Subject Disposition, Nicolle 2002 Study

Categories	Pivmecillinam 400 mg BID x 3 Days N=431, n (%)	Norfloxacin 400 mg BID x 3 Days N=429, n (%)
Completed study	322 (74.7)	346 (80.7)
Discontinued study	109 (25.3)	83 (19.3)
Adverse event	3 (0.7)	7 (1.6)
Failure to meet randomization criteria	5 (1.2)	7 (1.6)
Unacceptable treatment effect	72 (16.7)	39 (9.1)
Lost to follow-up	21 (4.9)	20 (4.7)
Other	7 (1.6)	8 (1.9)
Withdrawal by subject	1 (0.2)	1 (0.2)
Progressive disease	0 (0)	1 (0.2)
Death	0 (0)	0 (0)
Voluntary withdrawal	0 (0)	0 (0)

Source: adsl.xpt, statistical analyst; (Nicolle et al. 2002)

Abbreviations: BID, twice daily; N, number of subjects in treatment group; n, number of subjects with given characteristic

Concomitant medications were administered in 67% of pivmecillinam subjects and 71% of norfloxacin subjects at baseline with genito-urinary system and sex hormones being the most frequent concurrent drug treatment.

A mean number of six tablets were taken by subjects in the pivmecillinam and norfloxacin treatment arms in the Nicolle study. The Applicant stated that over 97% of subjects in the Nicolle study took study medication as described and nearly all subjects took the full tablet allocation. See [Table 31](#) for details.

Table 31. Compliance: Number of Tablets Taken, Safety Population, Nicolle 2002 Study

Categories	Pivmecillinam 400 mg BID N=479	Norfloxacin 400 mg BID N=467
Mean	6	5.9
SD	0.3	0.5
Median	6	6
Minimum	2	2
Maximum	6	6
Number ^a	414	416

Source: Table 36 in the Nicolle clinical study report; (Nicolle et al. 2002)

^a Subjects not returning medication package are not included.

Abbreviations: BID, twice daily; N, number of subjects in treatment group; SD, standard deviation

The results of the primary efficacy analyses of the Nicolle study are shown in [Table 32](#). The overall response in the pivmecillinam arm was significantly lower than the overall response in the norfloxacin arm, with lower bound of the 95% CI for treatment differences far below the NI margin of -10% specified in the FDA guidance document on uUTI ([August 2019](#)). Hence, NI for pivmecillinam relative to norfloxacin was not demonstrated according to this margin.

Table 32. Primary Efficacy Analysis of Overall Response, Micro-ITT Analysis Set, Nicolle 2002 Study (Micro-ITT Analysis Set)

Categories	Pivmecillinam 400 mg BID × 3 Days	Norfloxacin 400 mg BID × 3 Days
Success n/N (%)	114/205 (55.6%)	159/210 (75.7%)
Risk Difference	-20.1%	
95% CI for RD	-29.5%, -10.7%	
p-Value	<0.001	

Source: Statistical analyst and statistics reviewer; (Nicolle et al. 2002)

Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the microbiological ITT analysis set; n, number of subjects in the specified category; RD, risk difference; TID, three times daily

Other secondary efficacy endpoints (Clinical Response and Microbiological Response) were also observed to have similar trends to the primary efficacy endpoint, with nominally significantly lower response rates compared to cephalexin and lower bounds of 95% CIs of treatment differences well below -10%. The majority of subjects who were not classified as treatment successes were categorized as treatment failures, with relatively low rates of subjects classified as having indeterminate responses. See [Table 33](#) for details.

Table 33. Applicant's Reanalysis, Micro-ITT Analysis Set, Nicolle 2002 Study

Endpoint	Response at TOC	Pivmecillinam 400 mg BID 3 days N=205 n (%)	Norfloxacin 400 mg BID 3 days N=210 n (%)
Overall Response	Success	114 (55.6)	159 (75.7)
	Difference	-20.1	
	95% CI for the diff.	(-29.5, -10.7)	
Clinical Response	Failure	85 (41.5)	44 (21.0)
	Indeterminate	6 (2.9)	7 (3.3)
Microbiological Response	Success	129 (62.9)	166 (79.0)
	Difference	-16.1	
	95% CI for the diff.	(-25.2, -7.0)	
	Failure	65 (31.7)	33 (15.7)
	Indeterminate	11 (5.4)	11 (5.2)

Source: Table 20 in the ISE; (Nicolle et al. 2002)

Note: Confidence interval is calculated using the Wald method with a continuity correction.

Note: Percentages are calculated as n/N × 100.

Abbreviations: BID, twice daily; CI, confidence interval; diff, difference; ISE, integrated summary of effectiveness; ITT, intent-to-treat; N, number of subjects in the microbiological ITT analysis set; n, number of subjects in the specified category; TOC, test-of-cure visit

6.3. Key Efficacy Review Issues

6.3.1. Efficacy in Relation to Other Antimicrobial Comparators

Issue

Failure to demonstrate noninferiority in efficacy in relation to other antimicrobials.

Background

Primary efficacy reanalysis for the Menday and Nicolle studies failed to meet NI (using a 10% NI margin specified in the FDA guidance document on uUTI ([August 2019](#))). See [Table 34](#) and [Table 35](#) for details.

Table 34. Primary Efficacy Analysis of Overall Response, Micro-ITT Analysis Set, Menday 2000 Study

Categories	Pivmecillinam	Cephalexin
	200 mg BID × 3 Days	250 mg QID × 7 Days
Success n/N (%)	91/127 (71.7%)	100/132 (75.8%)
Risk difference	-4.1%	
95% CI for RD	-15.6%, 7.4%	
p-Value	0.482	

Source: Statistical Analyst and Statistics Reviewer; ([Menday 2000](#))

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the microbiological ITT analysis set; n, number of subjects in the specified category; RD, risk difference; QID, four times daily

Table 35. Primary Efficacy Analysis of Overall Response, Micro-ITT Analysis Set, Nicolle 2002 Study

Categories	Pivmecillinam	Norfloxacin
	400 mg BID x 3 Days	400 mg BID x 3 Days
Success n/N (%)	114/205 (55.6%)	159/210 (75.7%)
Risk difference	-20.1%	
95% CI for RD	-29.5%, -10.7%	
p-Value	<0.001	

Source: Statistical Analyst and Statistics Reviewer; ([Nicolle et al. 2002](#))

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the microbiological ITT analysis set; n, number of subjects in the specified category; RD, risk difference

Assessment

The Menday study may have been underpowered to evaluate noninferiority because of the sample size in the micro-ITT analysis set being smaller than the recommended 310 subject per treatment group according to the FDA guidance document on uUTI ([August 2019](#)). The study did not provide a strong signal for an efficacy deficit.

In addition to NI to norfloxacin not being demonstrated in the Nicolle study, pivmecillinam was also shown to be inferior to norfloxacin. However, an efficacy deficit may be less concerning in this study because the pivmecillinam 400 mg BID for 3 days regimen was observed to be the least effective regimen in the Ferry study and is not the regimen proposed for approval.

Conclusion

The Menday study did not meet NI and did not provide a strong signal for an efficacy deficit. The Nicolle study also did not meet NI and demonstrated inferiority to pivmecillinam. Of note, the pivmecillinam 400 mg BID for 3 days regimen was observed to be the least effective regimen in the Ferry study and is not the regimen proposed for approval. Additionally, the Menday and Nicolle studies were conducted before statistical methods used to demonstrate NI became standardized.

6.3.2. Longer-Term Efficacy Data for Two Primary Efficacy Studies

Issue

Timing of assessment for key secondary endpoints resulting in a lack of longer-term data for two primary studies.

Background

The FDA guidance document on uUTI ([August 2019](#)) notes the need for longer-term data 21 to 28 days post randomization.

Assessment

Assessments of key secondary endpoints were performed after 3 to 7 days of treatment which does not meet the stated objective of 21 to 28 days after randomization stated in Section 5c for this secondary endpoint in the FDA guidance document for uUTI ([August 2019](#)).

However, the Ferry and Nicolle studies had longer-term follow-up visits (Day 35 to 49) so one of the three primary studies appeared to have data supporting efficacy over the longer-term during follow-up. See [Table 36](#) for details.

Table 36. Sustained Overall Response at Follow-Up Visit, Micro-ITT Analysis Set, Ferry 2007, and Nicolle 2002 Studies

Overall Response Success*	Ferry (2007)				Nicolle (2002)	
	Pivmecillinam 200 mg TID x 7 days n (%)	Pivmecillinam 200 mg BID x 7 days n (%)	Pivmecillinam 400 mg BID x 3 days n (%)	Placebo n (%)	Pivmecillinam 400 mg BID x 3 days n (%)	Norfloxacin 400 mg BID x 3 days n (%)
Long-Term Follow-Up ¹	56/94 (59.6)	54/96 (56.3)	45/84 (53.6)	14/70 (20.0)	97/139 (69.8)	102/147 (69.4)
Sustained Response ²	49/94 (52.1)	47/96 (49.0)	38/84 (45.2)	10/70 (14.3)	97/139 (69.8)	101/147 (68.7)

Source: Table 29 in the ISE; (Nicolle et al. 2002; Ferry et al. 2007)

* For TOC, denominator represents number of subjects in microbiological ITT analysis set; for long-term follow-up and sustained response, denominator represents number of subjects with available data.

¹ Long-term follow-up visit at Days 35-49 (Ferry) or Day 39±5 days (Nicolle).

² Sustained response = success at both the TOC and long-term follow-up visit; sustained overall response was defined based on sustained clinical response and microbiologic response at the follow-up visit.

Abbreviations: BID, twice daily; ITT, intent-to-treat; n, number of subjects with overall response success; TID, three times daily; TOC, test-of-cure

Conclusion

Overall response at the time of long-term follow-up and sustained overall response for three pivmecillinam regimens versus placebo was demonstrated in the Ferry study. Overall response at the time of long-term follow-up and sustained overall response were observed to be similar for the pivmecillinam and norfloxacin arms in the Nicolle study. However, overall response at a longer term timepoint was not demonstrated in the Menday and Vik primary studies due to lack of available data.

6.3.3. Efficacy Against Pathogens Other Than *E. coli*, Including Producers of ESBLs

Issue

Efficacy against pathogens other than *E. coli*, including producers of ESBLs.

Background

The vast majority of subjects in the three primary studies (80 to 88% in each arm) had *E. coli* at baseline. Very small numbers of subjects were infected with pathogens other than *E. coli* so that there was insufficient sample size to detect statistically significant treatment differences in subjects with specific pathogens other than *E. coli*. However, by combining all other pathogens into a separate subgroup, there were sufficient subjects to detect nominally statistically significant treatment differences.

Overall response rates in the Ferry study for the three pivmecillinam arms were nominally significantly higher than placebo among the subgroup of subjects with *E. coli* infections and for both 200 mg pivmecillinam regimens compared to placebo among subjects who did not have *E. coli* infections. There was no observed nominally statistically significant difference in overall

responses between the pivmecillinam 400 mg BID for 3 days arm versus placebo among subjects who did not have *E. coli* infections in the Ferry study. See [Table 37](#) for details.

Table 37. Overall Responses by Presence or Absence of *E. coli* Infections, Micro-ITT Analysis Set, Ferry 2007 Study

Categories	Pivmecillinam 200 mg BID × 7 Days	Pivmecillinam 200 mg TID × 7 Days	Pivmecillinam 400 mg BID × 3 Days	Placebo
<i>E. coli</i> Infections				
Success n/N (%)	73/120 (60.8%)	77/122 (63.1%)	59/122 (48.4%)	12/111 (10.8%)
Risk difference	50%	52.3%	37.5%	
95% CI for RD	38.7%, 61.4%	41.1%, 63.5%	26.1%, 49%	
p-Value	<0.001	<0.001	<0.001	
Non-<i>E. coli</i> Infections				
Success n/N (%)	9/18 (50%)	8/15 (53.3%)	3/12 (25%)	2/23 (8.7%)
Risk difference	41.3%	44.6%	16.3%	
95% CI for RD	10.5%, 72.1%	11.4%, 77.9%	-17.1%, 49.7%	
p-Value	0.005	0.006	0.313	

Source: Statistical analyst and statistics reviewer's analysis; ([Ferry et al. 2007](#))

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the microbiological ITT analysis set; n, number of subjects in the specified category; RD, risk difference; TID, three times daily

Overall responses in the pivmecillinam and cephalexin arms in the Menday study were similar among subjects with *E. coli* infections but favored cephalexin, with the lower bound of the 95% CI below the NI margin of -10%. There was a greater difference in favor of cephalexin among subjects with non-*E. coli* infections, so NI was not demonstrated in either subgroup. See [Table 38](#) for details.

Table 38. Overall Responses by Presence or Absence of *E. coli* Infections, Micro-ITT Analysis Set, Menday 2000 Study

Categories	Pivmecillinam 200 mg BID × 3 Days	Cephalexin 250 mg QID × 7 Days
<i>E. coli</i> Infections		
Success n/N (%)	77/104 (74%)	84/110 (76.4%)
Risk difference	-2.3%	
95% CI for RD	-14.8%, 10.2%	
p-Value	0.752	
Non-<i>E. coli</i> Infections		
Success n/N (%)	14/23 (60.9%)	16/22 (72.7%)
Risk difference	-11.9%	
95% CI for RD	-43.6%, 19.9%	
p-Value	0.53	

Source: Statistical analyst and statistics reviewer's analysis; ([Menday 2000](#))

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the microbiological ITT analysis set; n, number of subjects in the specified category; QID, four times daily; RD, risk difference

Overall responses in the pivmecillinam arm were also nominally significantly higher than in the ibuprofen arm among the subgroup of subjects with *E. coli* infections and close to nominal statistical significance in favor of pivmecillinam in the small subgroup of subjects who did not have *E. coli* infections in the Vik study. See [Table 39](#) for details.

Table 39. Overall Responses by Presence or Absence of *E. coli* Infections, Micro-ITT Analysis Set, Vik 2018 Study

Categories	Pivmecillinam 200 mg TID × 3 Days	Ibuprofen 600 mg TID × 3 Days
<i>E. coli</i> Infections		
Success n/N (%)	60/88 (68.2%)	21/96 (21.9%)
Risk difference	46.3%	
95% CI for RD	32.4%, 60.2%	
p-Value	<0.001	
Non-<i>E. coli</i> Infections		
Success n/N (%)	9/17 (52.9%)	5/23 (21.7%)
Risk difference	31.2%	
95% CI for RD	-3%, 65.4%	
p-Value	0.052	

Source: Statistical analyst and statistics reviewer's analysis; ([Vik et al. 2018](#))

Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the microbiological ITT analysis set; n, number of subjects in the specified category; RD, risk difference; TID, three times daily

Sample sizes in other pathogen subgroups were too small to demonstrate nominally statistically significant differences between any of the treatment groups in the three primary studies. It was not possible to conduct subgroup analysis by pathogens that were producers of extended spectrum beta-lactamases (ESBLs) because this information was not collected in the studies. See [Table 40](#) for details.

Table 40. Overall Success at Test-of-Cure by Baseline Pathogen, Micro-ITT Analysis Set, Primary Efficacy Studies

	Ferry (2007)		Menday (2000)		Vik (2018)	
	Pivmecillinam 200 mg TID x 7 days (N=137) n/N1 (%)	Placebo (N=134) n/N1 (%)	Pivmecillinam 200 mg TID x 3 days (N=127) n/N1 (%)	Cephalexin 250 mg QID x 7 days (N=132) n/N1 (%)	Pivmecillinam 200 mg TID x 3 days (N=105) n/N1 (%)	Ibuprofen 600 mg TID x 3 days (N=119) n/N1 (%)
Gram-Negative						
Enterobacteriaceae						
Citrobacter koseri	N/A	N/A	N/A	N/A	N/A	0/2 (0.0)
Citrobacter species	1/1 (100.0)	0/2 (0.0)	1/1 (100.0)	N/A	N/A	N/A
Enterobacter species	1/2 (50.0)	1/5 (20.0)	1/1 (100.0)	1/1 (100.0)	1/3 (33.3)	1/2 (50.0)
Escherichia coli	77/121 (63.6)	10/107 (9.3)	77/104 (74.0)	82/107 (76.6)	60/88 (68.2)	21/96 (21.9)
Klebsiella pneumoniae	N/A	N/A	1/4 (25.0)	2/3 (66.7)	1/2 (50.0)	0/1 (0.0)
Klebsiella species	3/6 (50.0)	1/8 (12.5)	1/2 (50.0)	0/1 (0.0)	N/A	N/A
Proteus mirabilis	1/1 (100.0)	N/A	6/9 (66.7)	8/13 (61.5)	N/A	0/1 (0.0)
Gram-Positive						
Enterococcus faecalis	N/A	N/A	N/A	N/A	N/A	0/2 (0.0)
Enterococcus species	1/4 (25.0)	2/6 (33.3)	N/A	N/A	N/A	N/A
Staphylococcus aureus	1/2 (50.0)	0/1 (0.0)	N/A	1/1 (100.0)	N/A	N/A
Staphylococcus saprophyticus	1/2 (50.0)	0/6 (0.0)	4/7 (57.1)	6/6 (100.0)	7/12 (58.3)	4/15 (26.7)

Source: Table 23 in the ISE; ([Menday 2000](#); [Ferry et al. 2007](#); [Vik et al. 2018](#))

Note: Percentages are calculated as n/N1 × 100.

Abbreviations: ITT, intent-to-treat; N, number of subjects in the microbiological ITT analysis set; n, number of subjects with overall success at TOC visit; N1, number of subjects with specified baseline pathogen; N/A, not applicable; QID, four times daily; TID, three times daily; TOC, test-of-cure

Overall responses in the Nicolle study for the pivmecillinam arm in subgroups of subjects with and without *E. coli* infections were nominally significantly lower than overall responses in the norfloxacin arms, with the lower bound of the 95% CI far below -10% so NI was not demonstrated in either subgroup according to this margin. See [Table 41](#) for details.

Table 41. Overall Responses by Presence or Absence of *E. coli* Infections, Micro-ITT Analysis Set, Nicolle 2022 Study

Categories	Pivmecillinam 400 mg BID x 3 Days	Norfloxacin 400 mg BID x 3 Days
<i>E. coli</i> Infections		
Success n/N (%)	102/177 (57.6%)	140/187 (74.9%)
Risk difference	-17.2%	
95% CI for RD	-27.4%, -7.1%	
p-Value	<0.001	
Non-<i>E. coli</i> Infections		
Success n/N (%)	12/28 (42.9%)	19/23 (82.6%)
Risk difference	-39.8%	
95% CI for RD	-67.7%, -11.8%	
p-Value	0.005	

Source: Statistical analyst and statistics reviewer's analysis; ([Nicolle et al. 2002](#))

Abbreviations: BID, twice daily; CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the microbiological ITT analysis set; n, number of subjects in the specified category; RD, risk difference

Conclusion

Similar trends to those observed in the overall population were demonstrated in subgroups of subjects with *E. coli* infections and for all other subjects without *E. coli* infections combined. Nominally statistically significant treatment differences could not be demonstrated for individual specific pathogens other than *E. coli*. Nominally statistically significant differences could not be demonstrated for producers of ESBLs since data were not available to identify this subgroup.

7. Safety (Risk and Risk Management)

The overall assessment of safety of pivmecillinam was informed by a variety of sources, including nonclinical toxicology, safety pharmacology studies and clinical studies. The clinical safety analysis was based primarily on the three primary safety studies, i.e., Ferry 2007, Menday 2002, and Bresky 1977, with supportive data from Nicolle 2002, but was also informed by the postmarketing safety data from outside the U.S ([Bresky 1977](#); [Menday 2000](#); [Nicolle et al. 2002](#); [Ferry et al. 2007](#)).

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Nonclinical studies with pivmecillinam and MEC (including repeat dose toxicity studies in rats, dogs, and monkeys) did not demonstrate toxicities likely to be relevant to the clinical use of PIVYA, especially for short term use. The data from these studies with pivmecillinam and MEC show that PIVYA is expected to be reasonably safe for the proposed clinical indication when

used as directed. Thus, there is no objection to its approval from the pharmacology/toxicology review team.

Pivmecillinam is a prodrug of MEC providing oral bioavailability. Nonclinical pharmacology and toxicology studies have been conducted with both chemical entities. Many of these studies (except the genetic toxicology studies conducted by the current Applicant) were conducted prior to the adoption of good laboratory practice (GLP) regulations by (or on behalf of) the product originator, LEO Pharma A/S. There are also a few studies (not contemporary) conducted by (or on behalf of) Hoffman-LaRoche Inc (b) (4)

(b) (4) The Division agreed that these nonclinical studies would be acceptable to support the development and marketing of PIVYA in light of the previous favorable actions taken by FDA (b) (4)

(b) (4), and because there is extensive clinical experience with these drugs. Additionally, it was considered doubtful that repeating the nonclinical pharmacology/toxicology studies would provide additional relevant information important to the safety of PIVYA. The Applicant was advised to conduct a battery of genotoxicity studies with pivmecillinam and MEC, as these data were not available at the time of IND submission, and they are necessary to write a label for an approved product according to current standards.

Target Organs of Toxicity

Gastrointestinal Intolerance

Gastrointestinal intolerance (vomiting in dogs and monkeys and soft stool and occasional diarrhea in monkeys) was observed in studies with pivmecillinam (approximately one to three months of daily oral dosing). The doses used for these studies were about 7 to 10-fold higher than the daily human pivmecillinam dose with PIVYA based on body surface area.

Liver

Liver findings were seen in longer term studies (26 weeks) of pivmecillinam (oral dosing) and MEC (subcutaneous dosing) and were more prevalent in dogs than rats. No degenerative or necrotic changes were observed. In rats, the only findings were hepatocyte hypertrophy and increased cytoplasmic vacuolation. Some additional changes were seen in dogs, including intracytoplasmic basophilic and/or eosinophilic granules (MEC) and minimal to mild deposition of basophilic pigment in Kupfer cells (both drugs). Any of the transient clinical chemistry changes observed in dogs (aspartate aminotransferase, alanine aminotransferase, ALP) were reversed within a few weeks after dosing ceased. Although basophilic pigment persisted after a 25-week recovery period (especially in the MEC-treated animals that received a higher dose, when one considers the salt and prodrug linker of pivmecillinam), the other changes were reversible and there was no sign of any progressive liver toxicity in any animal (periodic biopsy performed during recovery period). It appears unlikely that these findings are relevant to the short-term use of these drugs in humans.

Kidney

The findings in kidney observed during a pivmecillinam 3-month monkey study and 6-month rat study and with MEC in a 3-month rat study appeared likely to be adaptive due to high renal excretion. In rats the only kidney finding was increased weight.

Genetic Toxicology

MEC is neither mutagenic nor clastogenic based on a standard battery of genotoxicity tests (Ames, clastogenicity in cultured human lymphocytes, in vivo mouse micronucleus). However, its bacterial toxicity limited the level that could be used in testing some of the *Salmonella* strains used in the Ames assay. Thus, (Q)SAR analysis was also used to confirm that MEC is unlikely to induce mutations. Although pivmecillinam is also negative in the in vivo mouse micronucleus assay, it is positive in the Ames assay and induces clastogenicity in cultured human lymphocytes. In light of the negative results with MEC, the positive results with pivmecillinam are considered likely to be due to the release of formaldehyde. In vivo, formaldehyde is quickly eliminated, but is present for a longer period in vitro. The positive results in the in vitro assays with pivmecillinam are not considered relevant to humans receiving PIVYA.

Reproduction and Developmental Toxicology

Results of reproduction toxicity studies with pivmecillinam (oral) and MEC (subcutaneous injection) did not reveal concerns regarding fertility (rats, 10.2/7.9-fold higher than PIVYA daily dose, for pivmecillinam and MEC, respectively), embryo-fetal development (rats, 3.4/7.9 and mice, 5.1/3.9) or pre and postnatal development (rats, 10.2/7.9). Fetotoxicity (reduced ossification of sternebrae) was observed in the offspring of dams given pivmecillinam at a dose approximately 10.2-fold higher than the recommended daily dose of PIVYA in a developmental toxicity study, but no drug-induced malformations were observed.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Pivmecillinam is a member of the beta-lactam class of antibacterial drugs, which are generally well-tolerated. The most common adverse reactions of this class include gastrointestinal disorders, including nausea, vomiting, diarrhea, and headache. Less common adverse reactions include rash/hypersensitivity reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, and *Clostridioides difficile*-associated diarrhea. Central nervous system abnormalities including seizures or disturbed consciousness, hepatotoxicity, renal toxicity, and hematologic reactions, including immune-mediated hemolytic anemia and coagulopathy are also noted with beta-lactam antibacterials.

Clinical studies of pivalate-conjugated antibacterials have demonstrated an increased risk of secondary carnitine deficiency and serious adverse reactions including death in subjects with primary carnitine deficiency ([Rasmussen 2013](#)). Pivmecillinam administration has been associated with acute symptoms of porphyria in susceptible individuals. Porphyrias are a group of rare disorders caused by an enzymatic defect in the heme biosynthetic pathway that can present with debilitating and sometimes life-threatening symptoms. Carnitine deficiency and porphyrias will be further discussed in Section [7.7](#).

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Additional data to support the safety assessment included postmarketing data from the PSUR Summary for MEC/pivmecillinam from Karo Pharma AB dated September 4, 2023, covering the period of July 1, 2022 to June 30, 2023, a comprehensive review of the medical literature, a meta-analysis of randomized clinical studies comparing the safety and efficacy of different pivmecillinam regimens for uUTI ([Pinart et al. 2017](#)), a review of the FDA Adverse Event Reporting System database, and ex-U.S. labels submitted by the Applicant. The Applicant also provided outcome data on pregnancy, lactation, and reproductive potential from the electronic safety database acquired from Leo Pharma on February 28, 2021, and data from the public European Medicines Agency safety database and aggregate (PSUR) data from the marketing authorization holder outside the U.S. (Karo Pharma AB), from February 28, 2021, until the NDA submission. A 120-day safety update was also provided by the Applicant on February 16, 2024. These data sources reported adverse events described in the three primary and one supportive safety studies submitted in the NDA (see Section [7.6](#) Safety Results) and identified adverse reactions generally consistent with other beta-lactam antibacterial drugs (see Section [7.2](#) Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors), including anaphylactic reactions, esophageal ulcers and esophagitis, cutaneous reactions such as urticaria, and *Clostridioides difficile*-associated diarrhea; see Section [23](#) Labeling: Key Changes and Considerations for additional details.

7.4. FDA Approach to the Safety Review

The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review. There are no major identified issues with respect to recording, coding, and categorizing adverse events (AEs). Definitions of TEAEs, grading of AEs (if performed) and limitations are discussed in Section [7.6](#) Safety Results under the individual studies. The Applicant's translation of verbatim terms to MedDRA preferred terms for the events reported in the primary and supportive safety studies ([Bresky 1977](#); [Menday 2000](#); [Nicolle et al. 2002](#); [Ferry et al. 2007](#)) was reviewed and found to be acceptable.

7.4.1. Sources of Data for Clinical Safety Assessment

The Applicant did not conduct any clinical studies but submitted study data acquired from other Sponsors. FDA's review focused on four randomized controlled studies that evaluated pivmecillinam in adults with uUTI ([Bresky 1977](#); [Menday 2000](#); [Nicolle et al. 2002](#); [Ferry et al. 2007](#)) for which safety data were available. Although the protocol for Vik 2018 included assessments of safety as well as efficacy, codes used by the authors to identify AEs were not available to the Applicant and therefore not submitted in this NDA ([Vik et al. 2018](#)).

FDA analysis did not pool studies as the dose, regimen, duration of therapy, use of a comparator, and inclusion/exclusion criteria differed significantly from study to study. The Applicant provided supportive safety data in seven additional studies. As these supportive studies had significant limitations in study design, e.g., were open-label, noncontrolled and nonrandomized and had safety findings consistent with the three primary and one supportive safety studies,

safety results from the additional seven supportive studies provided by the Applicant are not presented in this review.

Additional data to support the safety assessment included postmarketing data from Karo Pharma AB, review of the medical literature, a meta-analysis of randomized clinical studies ([Pinart et al. 2017](#)), outcome data on pregnancy, lactation, and reproductive potential, and public European Medicines Agency safety database as noted in Section [7.3](#) Potential Risks or Safety Concerns Identified Through Postmarket Experience.

The primary safety population included all randomized females 18 years of age or older who received at least one dose of the study drug. The Applicant translated verbatim terms to the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 for the events reported in all studies. The analysis of TEAEs used a cut-off date of Day 30.

The analysis focused on female subjects, as male subjects were considered to have complicated UTIs ([August 2019](#)). Although several of the submitted safety studies enrolled male subjects, including primary safety studies Munday 2000 and Bresky 1977, total numbers of male subjects and AEs were small, precluding a separate analysis ([Bresky 1977](#); [Munday 2000](#)).¹

An insufficient number of adolescent subjects, i.e., 16 to 17 years of age were enrolled to permit a separate assessment in this population.² The safety review was therefore limited to adult subjects (18 years of age or older).

Specifics regarding study design and AE monitoring are outlined in the individual discussions of safety results, see Section [7.6](#) Safety Results.

7.4.2. Reviewer Approach to Safety Evaluation

Clinical data were independently analyzed using R software. All safety assessments and conclusions are those of the FDA clinical review team unless otherwise specified.

7.5. Adequacy of the Clinical Safety Database

The four safety studies were missing some data variables commonly evaluated in safety analyses, including demographic data on race and ethnicity, medical history, concomitant medications other than antibacterials used for rescue treatments, laboratory evaluations, vital signs, and adverse events leading to modifications of the study drug. Demographic information on race/ethnicity was only available for the Munday study. Data on study discontinuation were available for the Ferry and Nicolle studies. Additional details are provided in Section [7.6](#) Safety Results, under individual study safety results.

Despite these limitations, overall data on the dosing, duration of exposure and number of subjects in the database were sufficient to conduct a safety review of pivmecillinam in adult females for the uUTI indication. While the majority of subjects in the primary safety studies

¹ Most male subjects (n=13) were enrolled in Bresky 1977 and only one subject, in the open-label, non-randomized, non-comparator arm, reported AEs (abdominal pain upper, and nausea).

² A total of 18 subjects 16-17 years of age were enrolled in the four safety studies; none of the patients assigned to the pivmecillinam group reported AEs,

were enrolled from Europe ([Bresky 1977](#); [Nicolle et al. 2002](#); [Ferry et al. 2007](#)), one study ([Menday 2000](#)) included 213 subjects from the U.S. who received pivmecillinam at the proposed dose and regimen.

The safety database in this NDA submission contained subject level data from phase 3 studies as follows:

- 495 subjects who received pivmecillinam at the proposed dose of 200 mg TID for 3 to 7 days ([Menday 2000](#); [Ferry et al. 2007](#))
- 579 subjects who received pivmecillinam 200 mg TID for 3 to 10 days ([Bresky 1977](#); [Menday 2000](#); [Ferry et al. 2007](#))
- 1753 subjects who received pivmecillinam at all doses and regimens ([Bresky 1977](#); [Menday 2000](#); [Nicolle et al. 2002](#); [Ferry et al. 2007](#))

7.6. Safety Results

7.6.1. Overall Safety Results From Ferry 2007, Menday 2000, Bresky 1977, and Nicolle 2002 Studies

In general, pivmecillinam was well-tolerated with a safety profile similar to that of other beta-lactam antibacterial drugs. No deaths or serious adverse events (SAEs) were observed in subjects receiving pivmecillinam.

At the proposed dose and regimen of 200 mg TID for 3 to 7 days, the overall incidence of TEAEs was 16.7% in subjects receiving pivmecillinam and 11.1% in placebo recipients ([Ferry et al. 2007](#)); and a lower incidence (6%) in pivmecillinam compared to cephalexin recipients (7%) ([Menday 2000](#)). AEs occurring in >1% of recipients and more frequently in the pivmecillinam group than the comparator, were nausea (4.3%), diarrhea (2.1%), vulvovaginal candidiasis (1.8%), pruritis genital (1.8%), and headache (1.4%) ([Ferry et al. 2007](#)); and nausea in 3/213 (1.4%) ([Menday 2000](#)). These AEs could be plausibly related to the study drug. Datasets for only two studies recorded study discontinuation due to AEs. In the Ferry study, two subjects in the pivmecillinam 200 TID group discontinued treatment due to hemorrhagic diarrhea and vomiting. In Nicolle 2002, three subjects discontinued pivmecillinam 400 mg BID due to rash, somnolence and back pain ([Nicolle et al. 2002](#)). No safety signals were identified in subgroup analyses or from the higher dosage regimens. Laboratory assessments were available from only one study ([Menday 2000](#)); no significant changes from baseline were observed. See Section [7.6.3.2](#).

Safety data were evaluated for the symptoms of carnitine depletion and acute attacks of porphyria, due to the association of these conditions with pivmecillinam administration. No subjects with TEAEs consistent with these conditions were observed, although the primary safety studies were not powered to detect rare AEs. See Section [7.7](#) Key Safety Review Issues, for further details.

7.6.2. Safety Results, Ferry 2007 Study

The study was comprised of female subjects with a mean age of 41.5 to 44 years in each treatment arm with 14 to 19% aged 65 years and older. The study was conducted solely in Sweden. Race and ethnicity data were not available for this study. See [Table 42](#) for details.

Table 42. Baseline Demographic and Clinical Characteristics, Safety Population, Ferry 2007 Study

Characteristic	PIVYA 200 mg BID × 7 Days N=294	PIVYA 200 mg TID × 7 Days N=282	PIVYA 400 mg BID × 3 Days N=287	Placebo N=288
Sex, n (%)				
Female	294 (100)	282 (100)	287 (100)	288 (100)
Age, years				
Mean (SD)	43.6 (17.6)	44 (18.2)	43.7 (18.3)	41.5 (17.4)
Median (min, max)	44 (18, 85)	41 (18, 82)	42 (18, 88)	39 (18, 83)
Age group, years, n (%)				
≤24	60 (20.4)	62 (22)	61 (21.3)	67 (23.3)
25 to <50	120 (40.8)	111 (39.4)	126 (43.9)	127 (44.1)
≥50	114 (38.8)	109 (38.7)	100 (34.8)	94 (32.6)
Age group ≥65, years, n (%)				
≥65	47 (16)	52 (18.4)	55 (19.2)	41 (14.2)
Age group ≥75, years, n (%)				
≥75	10 (3.4)	13 (4.6)	16 (5.6)	14 (4.9)

Source: adsl.xpt; Software: R; ([Ferry et al. 2007](#))

Abbreviations: BID, twice daily; N, number of subjects in treatment group; n, number of subjects with given characteristic; PIVYA, pivmecillinam; SD, standard deviation; TID, three times daily.

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Ferry 2007 Study

See Section [3.2](#) Approach to the Clinical Review, [Table 3](#) for details on study design.

Adverse Event Monitoring

Ferry 2007 evaluated AEs on Days 8 to 19 and 35 to 49 ([Ferry et al. 2007](#)); see Section [3.2](#) Approach to the Clinical Review, [Table 3](#) for more details. Under the protocol, adverse events reported by the subject or observed by the investigator were recorded in terms of nature, severity and relationship to therapy.

Data Limitations

Demographic data on race and ethnicity, SAEs, laboratory evaluations, and vital signs, were not provided. While the datasets included AEs leading to discontinuation of study drug, other actions such as dose modification due to AEs were not reported.

Study Results

In the Ferry study, a total of 1172 subjects were enrolled, 1162 were randomized, and 1151 were included in the safety population.

No deaths were reported in this study.

At the proposed dose of pivmecillinam 200 mg TID for 7 days, 2 subjects (0.7%) in the pivmecillinam group experienced AEs leading to discontinuation of study drug: one subject with bloody diarrhea discontinued treatment on Day 2 and the second subject experienced vomiting and discontinued the pivmecillinam on Day 3.

Overall, TEAEs were observed in 16.7% of subjects receiving pivmecillinam at the proposed dose compared to 11.1% of placebo recipients. In the pivmecillinam 200 mg TID for 7 days group, 7 subjects (2.5%) reported severe TEAEs versus 4 (1.4%) placebo recipients. TEAEs classified as severe occurring in subjects in the pivmecillinam 200 mg TID group included two subjects with pruritis genital, and one subject each with diarrhea, fungal infection, breast cancer, vulvovaginal candidiasis, breast pain. TEAEs of breast cancer and breast pain were considered by the clinical investigator to be unrelated to the study treatment.

The only AE preferred term for which the risk difference between pivmecillinam and placebo was >1% was vulvovaginal candidiasis, see [Table 43](#). AEs by system organ class that occurred with a risk difference >1 in subjects treated with pivmecillinam 200 mg TID compared with placebo included gastrointestinal disorders and infections/infestations; see [Table 44](#). TEAE that occurred at a frequency of >1% more commonly in the pivmecillinam 200 mg TID group compared with placebo were nausea in 12 (4.3%) subjects, diarrhea in 6 (2.1%) subjects, vulvovaginal candidiasis in 5 (1.8%) subjects, pruritis genital in 5 (1.8%) subjects, and headache in 4 (1.4%) subjects; see [Table 43](#).

TEAEs that occurred <1% frequency in the pivmecillinam 200 mg TID group but were considered adverse reactions were abdominal pain in 2 (0.7%) subjects. Of note there were no reported cases of hypersensitivity reactions, severe cutaneous adverse reactions, toxic epidermal necrolysis, or rash in subjects receiving pivmecillinam.

The following table provides an overview of AEs, including AEs leading to study drug discontinuation and AEs by severity.

Table 43. Overview of Adverse Events, Safety Population, Ferry 2007 Study

Event Category	PIVYA 200 mg TID × 7 Days N=282, n (%)	PIVYA 200 mg BID × 7 Days N=294, n (%)	PIVYA 400 mg BID × 3 Days N=287, n (%)	Placebo N=288 n (%)
AE leading to permanent discontinuation of study drug	2 (0.7)	1 (0.3)	2 (0.7)	0
Any AE	47 (16.7)	33 (11.2)	37 (12.9)	32 (11.1)
Severe and worse	7 (2.5)	5 (1.7)	2 (0.7)	4 (1.4)
Moderate	22 (7.8)	16 (5.4)	15 (5.2)	8 (2.8)
Mild	18 (6.4)	12 (4.1)	20 (7)	20 (6.9)

Source: adae.xpt; Software: R; ([Ferry et al. 2007](#))

Notes:

- Treatment-emergent adverse events defined as an adverse event occurring up through Day 30.
- Duration is median 7 days (maximum 46 days, minimum 1 day).
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- Severity assessed by the investigator.

Abbreviations: AE, adverse event; BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with at least one event; PIVYA, pivmecillinam; TID, three times a day

7.6.2.2. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Ferry 2007 Study

TEAEs by FDA Medical Query leading to treatment discontinuation are shown below. All subjects discontinuing study drug had AEs in the system organ class of gastrointestinal disorders and received pivmecillinam rather than placebo control. See [Table 44](#) for details.

Table 44. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Ferry 2007 Study

System Organ Class (SOC) Preferred Term	PIVYA 200 mg TID × 7 Days N=282, n (%)	PIVYA 200 mg BID × 7 Days N=294, n (%)	PIVYA 400 mg BID × 3 Days N=287, n (%)	Placebo N=288 n (%)
Any AE leading to discontinuation	2 (0.7)	1 (0.3)	2 (0.7)	0
Gastrointestinal disorders	2 (0.7)	1 (0.3)	2 (0.7)	0
Diarrhea hemorrhagic	1 (0.4)	0	0	0
Vomiting	1 (0.4)	0	0	0
Abdominal pain	0	1 (0.3)	0	0
Diarrhea	0	0	1 (0.3)	0
Nausea	0	1 (0.3)	1 (0.3)	0

Source: adae.xpt; Software: R; ([Ferry et al. 2007](#))

Notes:

- Treatment-emergent adverse events defined as an adverse event occurring up through Day 30.
- Duration is median 7 days (maximum 46 days, minimum 1 day).

Abbreviations: AE, adverse event; BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with adverse event; PIVYA, pivmecillinam; SOC, system organ class; TID, three times daily

7.6.2.3. Treatment-Emergent Adverse Events, Ferry 2007 Study

TEAEs occurring >1% are provided in the table below; see [Table 45](#).

Table 45. Subjects With Common Adverse Events >1% (Any Pivmecillinam Treatment Group), Safety Population, Ferry 2007 Study

Preferred Term	PIVYA 200 mg TID × 7 Days N=282, n (%)	PIVYA 200 mg BID × 7 Days N=294, n (%)	PIVYA 400 mg BID × 3 Days N=287, n (%)	Placebo N=288 n (%)
Any AE	47 (16.7)	33 (11.2)	37 (12.9)	32 (11.1)
Nausea	12 (4.3)	5 (1.7)	6 (2.1)	6 (2.1)
Vulvovaginal candidiasis	5 (1.8)	3 (1)	3 (1)	0
Diarrhea	6 (2.1)	5 (1.7)	9 (3.1)	2 (0.7)
Headache	4 (1.4)	0	3 (1)	1 (0.3)
Pruritus genital	5 (1.8)	3 (1)	3 (1)	4 (1.4)
Abdominal pain	2 (0.7)	3 (1)	2 (0.7)	1 (0.3)
Fatigue	2 (0.7)	3 (1)	2 (0.7)	3 (1)

Source: Adapted from CDS Table 13 - adae.xpt; Software: R; ([Ferry et al. 2007](#))

Notes:

- Treatment-emergent adverse events defined as an adverse event occurring up through Day 30.
- Serious adverse events defined as any untoward medical occurrence that at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
- Duration is median 3 days (maximum 34 days, minimum 1 day).

Abbreviations: AE, adverse event; BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with adverse event; PIVYA, pivmecillinam; SOC, system organ class; TID, three times daily

[Table 46](#) includes the incidence of AEs by system organ class, i.e., gastrointestinal disorders and infections/infestations, in subjects treated with pivmecillinam 200 mg TID compared with placebo.

There was one case of breast cancer reported in the pivmecillinam 200 mg TID group and none in the other groups. This AE was reported on Study Day 20 and was not reported as a pre-existing condition. However, the study investigator concluded this AE was unlikely to be related to the study drug and the review team agreed with this assessment.

Table 46. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow) and Preferred Term, Safety Population, Ferry 2007 Study

System Organ Class (SOC) Preferred Term	PIVYA 200 mg TID × 7 Days N=282, n (%)	PIVYA 200 mg BID × 7 Days N=294, n (%)	PIVYA 400 mg BID × 3 Days N=287, n (%)	Placebo N=288 n (%)
Any AE	47 (16.7)	33 (11.2)	37 (12.9)	32 (11.1)
Gastrointestinal disorders	25 (8.9)	18 (6.1)	19 (6.6)	13 (4.5)
Nausea	12 (4.3)	5 (1.7)	6 (2.1)	6 (2.1)
Diarrhea	6 (2.1)	5 (1.7)	9 (3.1)	2 (0.7)
Abdominal pain	2 (0.7)	3 (1)	2 (0.7)	1 (0.3)
Diarrhea hemorrhagic	1 (0.4)	0	0	0
Dry mouth	1 (0.4)	0	1 (0.3)	0
Gastritis	1 (0.4)	2 (0.7)	1 (0.3)	0
Dyspepsia	0	1 (0.3)	0	0
Oral mucosal eruption	0	1 (0.3)	0	0
Constipation	1 (0.4)	1 (0.3)	0	2 (0.7)
Vomiting	1 (0.4)	1 (0.3)	1 (0.3)	2 (0.7)
Gastric dilatation	0	0	0	1 (0.3)
Infections and infestations	9 (3.2)	10 (3.4)	3 (1)	1 (0.3)
Vulvovaginal candidiasis	5 (1.8)	3 (1)	3 (1)	0
Fungal infection	2 (0.7)	0	0	0
Vaginal infection	2 (0.7)	1 (0.3)	0	0
Erysipelas	0	1 (0.3)	0	0
Gastroenteritis	0	3 (1)	0	0
Infectious mononucleosis	0	1 (0.3)	0	0
Rhinitis	0	1 (0.3)	0	0
Upper respiratory tract infection	0	1 (0.3)	0	1 (0.3)

Source: adae.xpt; Software: R; ([Ferry et al. 2007](#))

Notes:

- Treatment-emergent adverse events defined as an adverse event occurring up through Day 30.
- Duration is median 7 days (maximum 46 days, minimum 1 day).
- Not all PTs are associated with an FMQ.
- Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Abbreviations: AE, adverse event; BID, twice daily; FDA, U.S. Food and Drug Administration; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PIVYA, pivmecillinam; PT, preferred term; SOC, system organ class; TID, three times daily

7.6.3. Safety Results, Menday 2000 Study

See Section [3.2](#) Approach to the Clinical Review, [Table 3](#) for details on study design.

Adverse Event Monitoring

In Menda 2000, follow-up for AEs was performed on Days 2/3, Day 10 $\pm$ 2 days, and Day 14 $\pm$ 2 days. Investigators recorded all clinical adverse effects reported and graded their severity on a three-point scale (mild, moderate, severe). Laboratory tests, including hemoglobin, hematocrit, white cell count, platelet count, BUN, creatinine, SGOT, SGPT, alkaline phosphatase, bilirubin, and urinalysis, were performed at baseline and at the end of treatment. Note: Menda 2000 was the only primary safety study that submitted laboratory data.

Data Limitations

Datasets submitted with this NDA were missing data on SAEs, AE severity, AEs leading to discontinuation, action taken with respect to study treatment following an AE, and vital signs.

Study Results

In the Menda study, a total of 441 subjects were enrolled, 441 were randomized, and 432 were included in the safety population, conducted in the U.S.

No deaths were reported in this study.

Overall, TEAEs were observed less commonly in subjects receiving pivmecillinam (13/213, 6.1%) compared to comparator (16/219, 7.3%). Severe TEAEs were observed at the same rate in the pivmecillinam arm as cephalexin (0.5%), while moderate TEAEs were observed less commonly in the pivmecillinam group (2.8%) compared to the cephalexin group (4.1%). The single subject in the pivmecillinam group with a TEAEs classified as severe had nausea that was considered possibly related to the study medication.

TEAEs that occurred in $>1\%$ of subjects and more commonly in the pivmecillinam arm included nausea in 3/213 (1.4%) compared with cephalexin in 1/219 (0.5%). There were no TEAEs for which the risk difference between pivmecillinam and cephalexin was $>1\%$. TEAEs observed at $<1\%$ frequency (each in 1/219, 0.5%) in the pivmecillinam arm included fungal infection, rash, vomiting, abdominal discomfort, constipation, eye irritation and odynophagia; see [Table 47](#). Fungal infection, rash and vomiting are included in the proposed labeling. Of note, there were no reported cases of hypersensitivity reactions reported in the pivmecillinam arm.

7.6.3.1. Treatment-Emergent Adverse Events, Menday 2000 Study

TEAEs occurring more commonly in pivmecillinam compared to cephalexin are shown in the table below.

Table 47. Subjects With Common Adverse Events, Safety Population, Menday 2000 Study

Preferred Term	PIVYA 200 mg TID × 3 Days N=213, n (%)	Cephalexin 250 mg QID × 7 Days N=219, n (%)
Any AE	13 (6.1)	16 (7.3)
Nausea	3 (1.4)	1 (0.5)
Abdominal discomfort	1 (0.5)	0
Constipation	1 (0.5)	0
Eye irritation	1 (0.5)	0
Fungal infection	1 (0.5)	0
Odynophagia	1 (0.5)	0
Rash	1 (0.5)	0
Vomiting	1 (0.5)	0

Source: adae.xpt; Software: R; ([Menday 2000](#))

Notes:

- Treatment-emergent adverse events defined as an adverse event occurring up through Day 30.
- Duration is median 7 days (maximum 15 days, minimum 2 days) for PIVYA.
- Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PIVYA, pivmecillinam; QID, four times daily; TID, three times daily

TEAE observed in >1% of subjects (both pivmecillinam and cephalexin arms) are presented in the [Table 48](#) below.

Table 48. Subjects With Common Adverse Events > 1%, Safety Population, Menday 2000 Study

Preferred Term	PIVYA 200 mg TID × 3 Days N=213, n (%)	Cephalexin 250 mg QID × 7 Days N=219, n (%)
Any AE	13 (6.1)	16 (7.3)
Nausea	3 (1.4)	1 (0.5)
Diarrhea	3 (1.4)	4 (1.8)
Vulvovaginal candidiasis	0	3 (1.4)

Source: adae.xpt; Software: R; ([Menday 2000](#))

Notes:

- Treatment-emergent adverse events defined as an adverse event occurring up through Day 30.
- Duration is median 7 days (maximum 15 days, minimum 2 days) for PIVYA.
- Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PIVYA, pivmecillinam; QID, four times daily; TID, three times daily

7.6.3.2. Laboratory Findings, Menday 2000 Study

Laboratory evaluations submitted from this study included hemoglobin, hematocrit, white cell count and differential, platelet count, BUN, creatinine, SGOT, SGPT, alkaline phosphatase, bilirubin, and urinalysis. No significant changes from baseline were observed for these parameters. Serum chemistries were not obtained.

For an analysis of AEs associated with renal function, see Section [7.6.3.5](#).

7.6.3.3. Assessment of Drug-Induced Liver Injury, Menday 2000 Study

None of the subjects in any of the treatment groups met biochemical Hy's Law criteria. A drug-induced liver injury assessment identified one subject in the Temple's Corollary quadrant who received pivmecillinam 200 mg TID for 3 days. This subject's laboratory values were normal except for baseline alanine aminotransferase 120 (180 at Day 10) and baseline aspartate aminotransferase 54 (105 at Day 10); bilirubin was normal at 0.3 and 0.4, respectively. Per the case report form, this subject was being evaluated for pre-existing hepatitis (laboratory results not provided).

7.6.3.4. Subgroup Analyses, Menday 2000 Study

The Menday study was the only study for which data on race and ethnicity were collected (race and ethnicity were combined). [Table 49](#) provides the AEs observed by age and race/ethnicity. No clear trends in AEs were observed according to age or race/ethnicity.

Table 49. Overview of Adverse Events by Demographic Subgroup, Safety Population, Menday 2000 Study

Characteristic	PIVYA 200 mg TID × 3 Days N=213, n/N _s (%)	Cephalexin 250 mg QID × 7 Days N=219, n/N _s (%)
Age group, years		
≤24	6/109 (5.5)	6/113 (5.3)
25 to <50	6/80 (7.5)	9/78 (11.5)
≥50	1/24 (4.2)	1/28 (3.6)
Age group ≥65, years, n/N _s (%)		
≥65	1/19 (5.3)	0/17 (0)
Age group ≥75, years, n/N _s (%)		
≥75	1/5 (20)	0/8 (0)
Race/ethnicity		
Asian	0/4 (0)	1/3 (33.3)
Black	1/24 (4.2)	3/28 (10.7)
White	12/180 (6.7)	12/186 (6.5)
Hispanic	0/3 (0)	0/2 (0)
Other	0/1 (0)	0/0 (N/A)

Source: adae.xpt and Menday.xpt; Software: R; ([Menday 2000](#))

Note: Categorization of race (Asian, Black, Caucasian, Other) and ethnicity (Hispanic) was combined in this study.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; N/A, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; PIVYA, pivmecillinam; QID, four times daily; TID, three times daily

7.6.3.5. Adverse Events in Subjects With Impaired Renal Function, Menday 2000 Study

While the protocol excluded subjects with significant renal impairment, [Table 50](#) provides subjects with abnormal renal function by calculated eGFR. Subjects with Level 1 (eGFR decrease of ≥25%) or Level 2 (eGFR decrease ≥50%) did not report any AEs.

Table 50. Subjects With Abnormal eGFR, Safety Population, Menday 2000 Study

Laboratory Parameter	PIVYA 200 mg TID × 3 Days N=213, n/N _w (%)	Cephalexin 250 mg QID × 7 Days N=219, n/N _w (%)
eGFR, low (mL/min/1.73 m ²)		
Level 1 (≥25% decrease)	8/165 (4.8)	20/177 (11.3)
Level 2 (≥50% decrease)	1/165 (0.6)	1/177 (0.6)
Level 3 (≥75% decrease)	0/165 (0)	0/177 (0)

Source: adlb.xpt; Software: R; ([Menday 2000](#))

Notes:

- Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).
- Duration is median 7 days (maximum 15 days, minimum 2 days) for PIVYA.
- Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
- In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
- eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation. Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PIVYA, pivmecillinam; QID, four times daily; TID, three times daily

7.6.4. Safety Results, Bresky 1977 Study

See Section [3.2](#) Approach to the Clinical Review, [Table 3](#) for study design.

Adverse Event Monitoring

Adverse events were collected (yes, no, comments if any) three to four days post-treatment but timing of AE relative to study drug administration, severity of AE, and SAEs were not recorded. The Applicant made no distinction between AEs and TEAEs; all reported AEs were assumed to be TEAEs.

Data Limitations

Datasets submitted with this NDA were missing demographic information (race and ethnicity), SAEs, AE severity, action taken following an AE (including study discontinuation or dose modification), AE start and end date, and relatedness to the study drug.

Of note, the study group receiving pivmecillinam 200 mg TID for 10 days was an open-label, no comparator extension. This treatment was conducted nonconcurrently to the comparator arm.

Study Results

In Bresky 1977, a total of 374 subjects were enrolled in Sweden, 374 were randomized, and 340 were included in the safety population ([Bresky 1977](#)).

No deaths were reported in this study.

Overall, TEAEs were observed less commonly in subjects receiving pivmecillinam at 200 mg TID for 10 days (5/84, 6%) compared to amoxicillin 375 mg TID for 10 days (30/142, 21.1%).

TEAEs that occurred in >1% of subjects and more commonly in the pivmecillinam 200 mg TID arm and plausibly related to the study drug was nausea (3/84, 3.6%). In the pivmecillinam 200 mg TID arm, no TEAEs were observed at <1%. In subjects receiving pivmecillinam 400 mg TID for 10 days, the following AEs were observed in > 1% of subjects: nausea (7.7%), dyspepsia (4.4%), abdominal pain, upper (4.4%), pruritis (2.6%), esophageal pain (1.8%) and rash (1.8%). One subject (#(b) (6)) who received 400 mg TID for 10 days experienced a toxic skin eruption. The

verbatim description was as follows: “after 3 days treatment universal itching and a rash predominantly located to the back... The skin reaction was of toxico-dermia type.” The study drug was discontinued on Day 4.

7.6.4.1. Treatment-Emergent Adverse Events, Bresky 1977 Study

Adverse events occurring in >1% of the population are provided in [Table 51](#).

Table 51. Subjects With Common Adverse Events >1%, Safety Population, Bresky 1977 Study

Preferred Term	PIVYA 200 mg TID × 10 Days N=84, n (%)	PIVYA 400 mg TID × 10 Days N=114, n (%)	Amoxicillin 375 mg TID × 10 Days N=142, n (%)
Any AE	5 (6)	25 (21.9)	30 (21.1)
Nausea	3 (3.6)	9 (7.9)	3 (2.1)
Conjunctivitis	1 (1.2)	0	0
Dysphagia	1 (1.2)	1 (0.9)	0

Source: Adapted from CDS table 13 -adae.xpt; Software: R; ([Bresky 1977](#))

Notes:

- Treatment-emergent adverse events defined as any adverse event that occurred during study (all AE start/end dates are missing).
- Duration is median 10 days (maximum 10 days, minimum 2 days).
- Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PIVYA, pivmecillinam; TID, three times daily

Reviewer Comments: In addition to the two pivmecillinam subjects with AEs of dysphagia noted above (one received 200 mg TID and the second received 400 mg TID), two additional subjects in the pivmecillinam groups had AEs of esophageal pain (both received 400 mg TID.) In the integrated summary of safety, Section 11.13.2, the Applicant asserted that the AEs of esophagitis were observed less frequently with the current (b) (4) formulation compared with the original tablet formulation. The capsule formulation was used in the Bresky study. The Applicant noted in M2.7.1 Section 2.2.21 that the capsule formulation was replaced in 1977 with the (b) (4) formulation. The Applicant also noted that the 400 mg tablets are larger (5 x 17 mm in diameter) compared with the 200 mg tablet (9.6 x 9.6 mm in diameter), and were more likely to be associated with difficulty in swallowing. In the integrated summary of safety, Section 11.13.12, the Applicant reported that Post Marketing Adverse Events of Interest observed during the entire postmarketing surveillance period (1900 through June 2023) included esophageal ulcer, esophagitis ulcerative, and erosive esophagitis; see Section 7.3 Potential Risks or Safety Concerns Identified Through Postmarket Experience.

[Table 52](#) provides an overview of AEs by age. No specific patterns were observed, although study size was small and not powered to detect differences by age group.

Table 52. Overview of Adverse Events by Demographic Subgroup, Safety Population, Bresky 1977 Study

Characteristic	PIVYA 200 mg TID x 10 Days N=84, n/N _s (%)	PIVYA 400 mg TID x 10 Days N=114, n/N _s (%)	Amoxicillin 375 mg TID x 10 Days N=142, n/N _s (%)
Age group, years			
≤24	0/16 (0)	12/33 (36.4)	8/43 (18.6)
25 to <50	2/39 (5.1)	5/41 (12.2)	10/63 (15.9)
≥50	3/29 (10.3)	8/40 (20)	12/36 (33.3)
Age group ≥65, years			
≥65	0/9 (0)	2/11 (18.2)	6/14 (42.9)
Age group ≥75, years			
≥75	0/1 (0)	0/1 (0)	0/0 (N/A)

Source: adae.xpt; Software: R; ([Bresky 1977](#))

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; N/A, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; PIVYA, pivmecillinam; TID, three times daily

7.6.5. Safety Results, Nicolle 2002 Study

See Section [3.2](#) Approach to the Clinical Review, [Table 3](#) for study design.

This study evaluated pivmecillinam at 400 mg BID for 3 days. Given that the dose evaluated differs from the proposed dose of 200 mg TID for 3 to 7 days, this study was considered supportive for safety and was evaluated to assess if any trends were observed with the higher dose of pivmecillinam.

The mean and median age ranged from 36 to 39 in the two treatment arms with only 1 to 2% of the subjects aged 65 and older. The majority of subjects were from Great Britain, Canada and France.

Table 53. Baseline Demographics and Clinical Characteristics, Safety Population, Nicolle 2002 Study

Characteristic	PIVYA 400 mg BID x 3 Days N=479	Norfloxacin 400 mg BID x 3 Days N=467
Sex, n (%)		
Female	479 (100)	467 (100)
Age, years		
Mean (SD)	38.6 (13)	38.1 (13.2)
Median (min, max)	38 (18, 84)	36 (18, 79)
Age group, years, n (%)		
≤24	79 (16.5)	82 (17.6)
25 to <50	295 (61.6)	278 (59.5)
≥50	105 (21.9)	107 (22.9)
Age group ≥65, years, n (%)		
≥65	4 (0.8)	8 (1.7)
Age group ≥75, years, n (%)		
≥75	1 (0.2)	1 (0.2)
Race, n (%)		
Missing	479 (100)	467 (100)
Ethnicity, n (%)		
Missing	479 (100)	467 (100)

Characteristic	PIVYA 400 mg BID × 3 Days N=479	Norfloxacin 400 mg BID × 3 Days N=467
Country of participation, n (%)		
Canada	108 (22.5)	110 (23.6)
France	105 (21.9)	93 (19.9)
Great Britain	140 (29.2)	145 (31)
Others	126 (26.3)	119 (25.5)
Is in United States, n (%)		
Non-United States	479 (100)	467 (100)

Source: adsl.xpt, CDS Programmer; Software: R; (Nicolle et al. 2002)

Abbreviations: BID, twice daily; N, number of subjects in treatment group; n, number of subjects with given characteristic; PIVYA, pivmecillinam; SD, standard deviation

Adverse Event Monitoring

Subjects had follow-up on Day 4, Day 11, and Day 39; in case of worsening symptoms, subjects were instructed to return to the clinic at any time. This study recorded SAEs.

Data Limitations

Demographic data on race and ethnicity, laboratory evaluations and vital signs were missing. The datasets included AEs leading to discontinuation of study drug, but dose modifications due to AEs were not reported.

Study Results

In Nicolle 2002, a total of 963 subjects were enrolled, 954 were randomized, and 946 were included in the safety population (Nicolle et al. 2002). This multicenter study enrolled subjects from Austria, Belgium, Canada, Denmark, France, Ireland, the Netherlands, Switzerland, and the UK.

No deaths were reported in this study.

There were no SAEs in the pivmecillinam arm. AEs leading to discontinuation of the study drug occurred less commonly in subjects receiving pivmecillinam (3/479, 0.6%) than norfloxacin (8/467, 1.7%) and TEAEs were less frequently reported in subjects receiving pivmecillinam (159/479, 33.2%) compared to norfloxacin (167/467, 35.8%). Severe TEAEs were observed in 5.4% of the pivmecillinam recipients compared with 4.5% of the norfloxacin recipients. Severe AEs in the pivmecillinam group considered by the clinical investigator to be probably or possibly related to the study drug included nausea, headache, chills, pyrexia, diarrhea, fatigue, somnolence, vaginal discharge, and vomiting.

Overall, TEAEs in >1% of subjects occurred at a frequency of 159/479 (33.2%) in the pivmecillinam arm compared with 167/467 (35.8%) in the norfloxacin arm. TEAEs occurring more commonly in recipients of pivmecillinam included nausea 9.2%, headache 4.4%, diarrhea 2.7%, dizziness 2.5%, dyspepsia 1.9%, back pain 1.5%, and vertigo 1.5%. The only preferred term to occur with significantly greater frequency was vulvovaginal candidiasis in the norfloxacin arm. Of note, there were no reported cases of hypersensitivity reactions reported in the pivmecillinam arm for this study.

7.6.5.1. Treatment-Emergent Adverse Events, Nicolle 2002 Study

Subject with AEs observed in >1% of the population are displayed in [Table 54](#).

Table 54. Subjects With Common Adverse >1%, Safety Population, Nicolle 2002 Study

Preferred Term	PIVYA 400 mg BID × 3 Days N=479, n (%)	Norfloxacin 400 mg BID × 3 Days N=467, n (%)
Any AE	159 (33.2)	167 (35.8)
Nausea	44 (9.2)	28 (6)
Headache	21 (4.4)	17 (3.6)
Diarrhea	13 (2.7)	7 (1.5)
Dizziness	12 (2.5)	10 (2.1)
Abdominal pain	10 (2.1)	11 (2.4)
Dyspepsia	9 (1.9)	3 (0.6)
Back pain	7 (1.5)	3 (0.6)
Vertigo	7 (1.5)	4 (0.9)
Lethargy	6 (1.3)	6 (1.3)
Pyrexia	5 (1)	2 (0.4)
Vaginal discharge	5 (1)	2 (0.4)
Vomiting	5 (1)	4 (0.9)
Oropharyngeal pain	4 (0.8)	7 (1.5)
Abdominal pain upper	4 (0.8)	8 (1.7)
Fatigue	4 (0.8)	10 (2.1)
Vulvovaginal candidiasis	3 (0.6)	13 (2.8)
Dysmenorrhea	2 (0.4)	5 (1.1)
Cough	1 (0.2)	7 (1.5)

Source: adapted from CDS – Table 13 - adae.xpt; Software: R; ([Nicolle et al. 2002](#))

Notes:

- Treatment-emergent adverse events defined as an adverse event occurring up through Day 30.
- Duration is median 7 days (maximum 15 days, minimum 2 days) for PIVYA.
- Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; BID, twice daily; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PIVYA, pivmecillinam

No specific patterns were observed in the frequency of AEs by age group; see [Table 55](#).

Table 55. Overview of Adverse Events by Demographic Subgroup, Safety Population, Nicolle 2002 Study

Characteristic	PIVYA 400 mg BID × 3 Days N=479, n/N _s (%)	Norfloxacin 400 mg BID × 3 Days N=467, n/N _s (%)
Age group, years		
≤24	25/79 (31.6)	32/82 (39)
25 to <50	97/295 (32.9)	106/278 (38.1)
≥50	37/105 (35.2)	29/107 (27.1)
Age group ≥65, years		
≥65	1/4 (25)	3/8 (37.5)
Age group ≥75, years		
≥75	0/1 (0)	0/1 (0)

Source: adae.xpt; Software: R; ([Nicolle et al. 2002](#))

Abbreviations: BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; PIVYA, pivmecillinam

7.7. Key Safety Review Issues

7.7.1. Carnitine Deficiency

Issue

Clinical studies of pivalate-conjugated antibacterials (PCA) have demonstrated an increased risk of carnitine deficiency related to the pivoxil moiety.

Background

Pivmecillinam is a prodrug to which a pivoxil group is bound to improve absorption. Following oral administration, pivmecillinam is absorbed from the gastrointestinal tract and undergoes hydrolysis to MEC, the active form of the drug, resulting in formation of pivalate. Pivalate combines with free carnitine in the blood to form pivaloyl carnitine which is excreted in the urine. PCAs, including pivmecillinam, have been associated with significant adverse reactions related to marked decrease in serum carnitine in pediatric and adult subjects with primary or secondary carnitine deficiency. Hypocarnitinemia can occur with short term and with prolonged therapy and in patients at risk for carnitine depletion (severe renal impairment or decreased muscle mass) ([Rasmussen 2013](#)) with standard doses and durations ([Holme et al. 1989](#)). While long term use of pivmecillinam has been associated with symptomatic hypocarnitinemia in patients without known risk factors, no clinical effects have been reported following short term (less than ten days) use at recommended dosages.

Carnitine is essential for fatty acid oxidation. When fats cannot be utilized for gluconeogenesis, hypoglycemia may occur, which can be life-threatening. Primary carnitine deficiency is an autosomal recessive disorder that occurs in the U.S. at an estimated rate of approximately 1 in 121,609 ([Lefevre et al. 2023](#)). This condition results from mutations in the SLC22A5 gene that encodes the organic cation transporter type 2 (OCTN2), which is expressed primarily in skeletal and heart muscle, kidneys, and liver ([Adeva-Andany et al. 2017](#)). Defects in this gene lead to decreased reabsorption, causing diminished carnitine levels in muscles and the heart and increased carnitine loss by the kidneys. Clinical manifestations can occur at any age but are most common in infants or young children. Infants with undiagnosed primary carnitine deficiency may present with hypoglycemia, hyperammonemia, failure to thrive, muscle weakness, and Sudden Infant Death Syndrome. Undiagnosed primary carnitine deficiency in adults may present with skeletal myopathy, cardiomyopathy, liver dysfunction, and arrhythmias ([Wang et al. 2001](#)). Newborn screening programs for primary carnitine deficiency are performed routinely in the U.S. and in many parts of the world.

Secondary carnitine deficiency can occur due to decreased dietary intake, decreased intestinal absorption, decreased biosynthesis, or excessive losses in the urine ([Stanley 2004](#)). Conditions leading to secondary carnitine depletion include malnutrition or malabsorption of carnitine, hemodialysis, fatty acid oxidation disorders, some organic acidemias, and drugs that increase urinary excretion of carnitine ([Pons and De Vivo 1995](#)).

In addition to pivmecillinam, drugs with a pivoxil moiety include adefovir dipivoxil³ (approved in the U.S.), cefditoren-pivoxil (Spectracef) which was approved in the U.S. in 2001 but is no longer marketed, and pivampicillin and valproate pivoxil (both not approved in the U.S. but marketed outside the U.S.). Pivmecillinam tablets are approved in several countries outside the U.S.; see Section 3 Introduction for more details. There are multiple case reports and case series reporting symptomatic carnitine deficiency following PCAs, with subjects presenting with hypoglycemia, altered consciousness, seizures, and arrhythmias ([Kobayashi et al. 2016](#)). These reports include subjects with undiagnosed primary carnitine deficiency ([Rasmussen 2013](#)), secondary carnitine deficiency following prolonged administration of pivmecillinam ([Holme et al. 1989](#)), and secondary carnitine deficiency following three days of antibacterials in a subject with muscular dystrophy ([Ito et al. 2017](#)). In Japan, where PCAs including pivmecillinam, cefditoren pivoxil, ceferam pivoxil, and cefcapene pivoxil have been marketed, a safety alert was issued in 2012, regarding a warning of serious hypocarnitinemia and hypoglycemia in children treated with antibacterial drugs containing a pivoxyl group ([Pharmaceuticals and Medical Devices Agency 2012](#); [Pharmaceuticals and Medical Devices Agency 2020](#)). A retrospective cohort study of a medical and claims database in Japanese children one month to five years of age with at least one prescription of a PCA demonstrated that younger children, particularly those less than one year of age were susceptible to hypoglycemia secondary to PCAs ([Tatebe Yasuhisa et al. 2018](#)).

The UK Summary of Product Characteristics for Selexid (pivmecillinam) tablets includes the following special warnings and precautions for use:

- Selexid tablets should be used with caution for long-term or frequently-repeated treatment, due to the possibility of carnitine depletion. Symptoms of carnitine depletion include muscle aches, fatigue, and confusion.
- Concurrent treatment with valproic acid, valproate or other medication liberating pivalic acid should be avoided due to increased risk of carnitine depletion ([Electronic Medicines Compendium 2024](#)).

Assessment

The primary safety studies for this NDA did not evaluate carnitine levels or serum glucose. To evaluate the potential occurrence of carnitine deficiency in the studies submitted with the NDA, the clinical reviewer searched the AE datasets submitted in this NDA for any combination of hypoglycemia, fatigue, muscle pain, or confusion. No subjects were identified.

The Applicant for this NDA has proposed the following Contraindication:

- In subjects with genetic metabolism anomalies known to result in severe carnitine deficiency such as carnitine transporter defect, methylmalonic aciduria, or propionic acidemia (4.2)

³ In clinical trials of adefovir dipivoxil for the long-term treatment of HIV, patients received concurrent carnitine to offset the chronic losses as pivaloylcarnitine ([Kahn et al. 1999](#)). Efficacy and safety of adefovir dipivoxil with antiretroviral therapy: a randomized controlled trial. JAMA 282: 2305–2312.

The Applicant has proposed the following statement under Warnings and Precautions:

- Carnitine depletion: Long-term treatment with pivaloyloxymethyl esters such as pivmecillinam should be avoided due to an increased risk of carnitine depletion. Concurrent treatment with valproic acid, valproate, or other medications liberating pivalic acid should be avoided due to increased risk of carnitine depletion.

Conclusion

The review team proposes the following labeling for pivmecillinam:

- **Contraindications**
 - **4.2. Carnitine Deficiency**
 - PIVYA is contraindicated in patients with primary or secondary carnitine deficiency resulting from inherited disorders of mitochondrial fatty acid oxidation and carnitine metabolism, and other inborn errors of metabolism (e.g., methylmalonic aciduria, or propionic acidemia).
- **5. Warnings and Precautions**
 - **5.3 Carnitine Depletion:**
 - Clinical manifestations of carnitine depletion may occur with pivalate-containing compounds, including PIVYA. Symptoms of carnitine depletion include hypoglycemia, muscle aches, fatigue, and confusion. PIVYA is contraindicated in patients with primary or secondary carnitine deficiency due to inherited metabolic disorders known to cause carnitine depletion.
 - No clinical effects of decreased carnitine have been associated with short-term treatment of PIVYA. Clinically significant hypocarnitinemia has been observed in patients receiving long term treatment with pivmecillinam; PIVYA is not recommended when prolonged antibacterial treatment is necessary. The effects on carnitine concentrations of repeat short-term courses of PIVYA are not known. In patients at risk for reductions in serum carnitine (e.g., patients with significant renal impairment or decreased muscle mass), consider alternative antibacterial therapies. Avoid concurrent treatment with valproic acid, valproate or other pivalate-generating drugs due to increased risk of carnitine depletion [see *Drug Interaction (7.1)*].
- **8. Use in Specific Populations**
 - **8.4 Pediatric Use**
 - The safety and effectiveness of PIVYA have not been established in pediatric patients.
 - Carnitine Depletion**
 - Symptomatic hypocarnitinemia has been reported in pediatric patients outside the United States on long term pivmecillinam therapy. In these cases, irritability, altered mental status, fatigue, muscle weakness, and vomiting have been observed. PIVYA is not recommended when prolonged antibacterial treatment is necessary [See *Warnings and Precautions (5.3)*]. PIVYA is contraindicated in patients with primary or secondary carnitine deficiency [see *Contraindications (4)*].

7.7.2. Porphyria

Issue

During postmarketing experience outside the U.S., rare reports of porphyria have been associated with use of pivmecillinam.

Background

Porphyrias are a group of rare disorders caused by an enzymatic defect in the heme biosynthetic pathway that result in the accumulation of intermediate compounds and can present with debilitating and sometimes life-threatening symptoms. Onset is usually in the second to fourth decade of life ([Bonkovsky et al. 2014](#)). In the US fewer than 200,000 individuals in total are affected by porphyria (all forms) ([Ramanujam and Anderson 2015](#)). Symptoms vary widely depending on the type. Acute attacks can consist of pain, autonomic and peripheral neuropathy, and CNS symptomatology including encephalopathy. Pivmecillinam used for treatment of UTIs has been reported as a precipitating factor in acute attacks of porphyria ([Baumann and Kauppinen 2022](#)).

Assessment

Data from the four primary safety studies ([Bresky 1977](#); [Menday 2000](#); [Nicolle et al. 2002](#); [Ferry et al. 2007](#)) were reviewed for subjects with any combination of AEs for insomnia, agitation, abdominal pain, hallucinations, seizures, or hyponatremia, extremity pain, and paresis.

Conclusion

No subjects with TEAEs consistent with porphyria were observed, although the primary safety studies were not powered to detect rare AEs.

The review team agrees with the proposed Prescribing Information Section 4, Contraindications, that states that PIVYA should not be used by subjects with porphyria, as pivmecillinam use has been associated with acute attacks of this condition.

8. Therapeutic Individualization

8.1. Intrinsic Factors

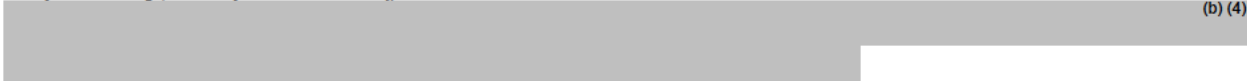
8.1.1. Renal Function

MEC is primarily eliminated via renal excretion with approximately 80% of the dose excreted in urine as MEC. MEC PK has been studied in subjects with renal impairment following intravenous (IV) MEC or oral pivmecillinam HCL (PIV) administration. Reductions in systemic elimination as well as urinary excretion of MEC were observed with increasing degrees of renal impairment in one study ([Nakano H. et al. 1977](#)), where single dose and multiple doses of 146.2 mg oral PIV HCL four times daily for seven days was administered to three group of subjects based on baseline creatinine clearance (CrCl). PK findings are summarized in [Table 56](#).

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PIVYA (pivmecillinam)

The study findings suggest a 21% and 152% increase in mean MEC maximum plasma concentration ($C_{\max}$) as well as a 25% and 314% increase in mean MEC area under the concentration-time curve (AUC) in subjects with CrCl 35-47 mL/min and 9-15 mL/min, respectively, compared to subjects with CrCl 73-84 mL/min. For more details see Section 14.2.7.



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Table 56. Summary of Mean (SD) MEC Serum and Urine Concentrations, PK Parameters, and Fold Change in Three Groups With Various Degrees of Renal Impairment After Oral Pivmecillinam HCL Administration

		Renal Impairment		
		Group #1 CrCl: 73-84 mL/min n=3	Group #2 CrCl: 35-47 mL/min n=3	Group #3 CrCl: 9-15 mL/min n=2
Categories	Dose			
Plasma PK				
C _{max} (µg/mL)	Single ^a	0.53 (0.19)	1.05 (1.06)	1.14
	Multiple ^b	0.79 (0.62)	0.96 (0.68)	1.99
C _{max} AR	Multiple/Single	1.49	0.91	1.74
C _{max} FC	Multiple #2 or #3/#1 ^c	–	1.21	2.52
AUC (µg•hr/mL)	Single ^{a, c}	1.51	2.73	5.10
	Multiple ^{b, c}	2.07	2.60	8.58
AUC AR	Multiple/Single ^c	1.4	0.95	1.68
AUC FC	Multiple #2 or #3/#1 ^c	–	1.25	4.14
Urine PK				
C _{max} (µg/mL)	Single ^a	75.7 (51.6)	33.7 (18.1)	14.6
	Multiple ^b	56.3 (24.2)	93.1 (79.7)	23.6
AR	C _{max} , multiple/C _{max} , single	0.74	2.75	1.61

Source: (Nakano H. et al. 1977), Tables 2 and 3, pg., 286 and Reviewer's independent analysis.

^a Plasma and urine were obtained after a single dose of 146. 2 mg PIV (equimolar to 100 mg MEC).

^b Plasma and urine were obtained after final dosing on Day 7 of 146. 2 mg PIV 4 times per day for a week.

^c Reviewer's independent analysis of mean data. Individual subject level data not available.

Abbreviations: (–), not calculated; AR, accumulation ratio; AUC, area under the concentration-time curve from time 0 to 6 hr after drug administration; C_{max}, maximum plasma concentration of drug; CrCl, creatinine clearance; FC, fold change; mean, arithmetic mean; MEC, mecillinam; n, number of subjects within group; SD, standard deviation; PK, pharmacokinetic

8.1.1.1. Evaluation of Applicant's Proposed

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The Applicant has proposed

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Overall, the review team concludes that no dose adjustment is needed based on the overall safety and effectiveness information summarized below.

From a safety perspective, for the recommended oral dosage of 200 mg PIV HCL TID for 3 to 7 days for the general population, the available information suggests no or low risk to subject safety due to MEC accumulation resulting from reduced renal function. Specifically, approximately 2 to 4-fold increase in systemic MEC exposures is anticipated in individuals with CrCl < 30 mL/min versus ≥ 90 -120 mL/min following administration of 200 mg PIV HCL TID for 3 to 7 days ([Table 56](#)). In clinical studies, MEC IV treatments of ≥ 400 mg every 4 or 6 hours (for ≥ 4 days) and single doses up to 15 mg/kg have been reported to be well-tolerated in subjects with normal renal function and with renal impairment (e.g., Patel et al. 1979, [Jansaker et al. 2018](#)). Given the low bioavailability of oral PIV tablet (25-35%), the MEC exposures associated with the MEC IV treatment are expected to be much greater than the exposures expected in subjects with CrCl <30 mL/min with the recommended 200 mg PIV HCL TID for 3 to 7 days oral dosage, the anticipated PK changes are therefore not expected to be clinically significant, and no dosage adjustment is needed from a safety perspective.

From an effectiveness perspective, there is a theoretical concern of clinical efficacy loss due to reduced MEC excretion in urine secondary to renal dysfunction. However, subjects with renal disease were largely excluded from the primary efficacy studies. The clinical significance of the anticipated decrease in MEC renal excretion on efficacy is unknown to inform specific dosage adjustment.

For additional details see Section [14.2.7](#) and Section [14.5.1](#)

8.1.2. Hepatic Function

The effects of hepatic impairment on the pharmacokinetics of PIV and MEC have not been evaluated. PIV is metabolized by nonspecific tissue and blood esterases. In vitro, MEC is not significantly metabolized. Furthermore, biliary excretion does not play a significant role in the elimination of MEC given the high cumulative excretion of unchanged MEC in urine (approximately 80% of intravenous dose). Therefore, hepatic impairment is not expected to have a clinically significant effect on PIV or MEC exposures, and no dosage adjustment is recommended based on hepatic function.

8.1.3. Other Intrinsic Factors

The effect of age, sex, race, and weight on the pharmacokinetics of MEC is unknown.

One study ([Ball et al. 1978](#)) evaluated MEC PK following PIV in 6 subjects greater than 65 years of age but did not include a comparator group.

PK data quality issues were identified during the review of this information and these issues limit the population PK model's application to evaluate the influence of these intrinsic factors (See Section [14.5.1](#))

8.2. Extrinsic Factors

8.2.1. Food Effect

Two studies were conducted to evaluate the effect of food on MEC PK when oral PIV HCL doses were administered with food in healthy adults (Bornemann, 1985, N2756A, Leo Pharma 1977). Administration with food slightly increased MEC bioavailability (approximately 25% based on AUC), but not to a clinically relevant extent. Therefore, PIV HCL oral tablets can be taken without regards to food.

For additional details see Section [14.2.5](#).

8.2.2. Drug Interactions

Carnitine Depletion

While no specific study has been conducted, concomitant use of PIV with pivalate-generating drugs (e.g., valproic acid) likely reduces L-carnitine concentrations in plasma, increasing the risk of carnitine depletion-associated adverse reactions. However, for the recommended three to seven days of drug therapy, the association between low plasma carnitine concentrations after pivalate-generating drug exposure, tissue carnitine content, and related toxicity is unknown ([Brass 2002](#)).

Therefore, the review team agrees with the Applicant that a statement should be included in Section 7 Drug Interactions of the product labeling. The review team recommends where possible, consideration of alternative medications that are not pivalate-generating drugs. If concomitant use with PIV is necessary, subjects should be counseled to monitor for adverse reactions associated with carnitine depletion (e.g., hypoglycemia, muscle aches, fatigue, and confusion).

Methotrexate

No specific drug interaction studies between methotrexate and PIV or MEC have been conducted. The Applicant proposes to include language in Section 7 Drug Interactions of the product labeling that methotrexate clearance can be reduced by penicillin class drugs. We agree with the Applicant's proposal as similar language is found in the piperacillin-tazobactam U.S. prescriber's information (same antibacterial class). We recommend with minor modifications to include the following statement in Section 7 Drug Interactions of the product labeling: "Clearance of methotrexate from the body can be reduced by concurrent use of penicillins, including PIV. Where possible, consider alternative therapy."

Effects of Other Drugs on the Pharmacokinetics of MEC

MATE1, MATE2K, and OAT3 inhibitors: Based on the published clinical study and in vitro study findings (summarized below), concomitant use of PIV with multidrug and toxin extrusion 1 (MATE1), 2K (MATE2K), and/or organic anion transporter 3 (OAT3) inhibitors (e.g., probenecid, cimetidine, trimethoprim, isavuconazole) is expected to increase MEC systemic AUC and C_{max} while also reducing urinary MEC concentrations.

The anticipated PK changes are not expected to be clinically significant, and no dosage adjustment is needed from a safety perspective. The clinical significance of these changes on efficacy is unknown to inform specific dosage adjustment.

8.2.2.1. Published Clinical Studies

Two published studies evaluated the effect of probenecid (OAT1/3 inhibitor) on MEC PK. Oral probenecid (inhibitor) increased the mean MEC AUC and C_{max} by approximately 40% and 80%, respectively, when administered concomitantly with PIV.

Based on the available safety information for IV MEC use and its rapid half-life (approximately one hour), the observed increase is not considered to be clinically significant to warrant a dosage adjustment from a safety perspective. However, due to a reduction in drug excreted in urine, there is a theoretical concern for efficacy loss.

Therefore, the review team does not agree with the Applicant's proposal to

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Therefore, the review team recommends including the qualitative DDI information summary in Section 12.3 Pharmacokinetics of product labeling. For additional details see Section [8.1.1.1](#) and Section [14.2.6](#).

8.2.2.2. In Vitro Studies

Cytochrome P450 (CYP) Enzymes: MEC does not inhibit nor induce metabolism mediated by CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Therefore, PIV is not expected to alter the pharmacokinetics of drugs metabolized by the above stated human hepatic enzymes. In addition, PIV and MEC are not CYP 450 enzyme substrates. For additional details see Section [8.1.2](#), Section [14.1.2](#), and Section [14.1.3](#).

Transporter Systems: MEC does not inhibit breast cancer resistance protein (BCRP), P-glycoprotein (PgP), multidrug and extrusion protein-1 (MATE1), multidrug and extrusion protein-2K (MATE2-K), organic anion transporter-1 (OAT1), organic anion transporter-3 (OAT3), organic anion transporting polypeptides -1B1 and 1B3 (OATP1 B1/B3) and organic cation transporter-2 (OCT2) drug transporters. MEC is a substrate of OAT3, MATE1, and MATE2-K. The Applicant submitted a published clinical study that further evaluated MEC's DDI potential as substrate of OAT3 transporter (summarized above), however, no clinical studies were performed, or information submitted on MEC's DDI potential with MATE1 and MATE2-K inhibitors. Therefore, the review team recommends that in addition to OAT3 inhibitors information, MATE1 and MATE2-K inhibitors be included in Section 12.3 of product labeling. For additional details see Section [14.1.4](#).

8.3. Plans for Pediatric Drug Development

The Applicant submitted an initial Agreed Pediatric Study Plan (iPSP) which was agreed upon on February 25, 2022.

On January 30, 2024, the PeRC reviewed and concurred with a partial waiver in children from birth to less than 2 months of age and with granting a deferral for the pediatric studies.

A postmarketing requirement to conduct a single dose study to assess the safety, tolerability and pharmacokinetics in pediatric subjects 2 months to less than 12 years of age receiving systemic antibacterial therapy for the treatment of a suspected or confirmed bacterial infection will be requested upon approval. This study will inform the population pharmacokinetic model to help select the dose and frequency for the pediatric safety and efficacy studies. Postmarketing requirements to conduct a single-blind study to evaluate the safety and tolerability of pivmecillinam hydrochloride versus nitrofurantoin for the treatment of pediatric subjects, 12 years to less than 18 years of age with uUTI and another study to evaluate the safety and tolerability of pivmecillinam with an appropriate comparator in subjects 2 months to less than 12 years of age with uUTI will be requested upon approval.

8.4. Pregnancy, Lactation, and Females / Males of Reproductive Potential

Pregnancy

Consultation was obtained from the Division of Pediatric and Maternal Health (DPMH) as well as the Division of Epidemiology to review the postmarketing and literature data submitted by the Applicant and to conduct a literature review for this Application. Refer to their review in DARRTS, dated March 20, 2024, and March 4, 2024, respectively.

Four observational studies were reviewed for evidence of increased risk of adverse pregnancy, maternal, and infant outcomes among pregnant women exposed to pivmecillinam ([Norgaard et al. 2008](#); [Nordeng et al. 2013](#); [Damkier et al. 2019](#); [Hjorth et al. 2022](#)). These studies were limited by potential exposure classification, outcome misclassification, and unmeasured confounding affecting interpretability. Among these, two cohort studies did not support an association between pivmecillinam use during the first trimester and the risk of malformations. There was insufficient evidence in the literature to confirm or refute increased risk of miscarriage following exposure to pivmecillinam. The other reviewed studies could not definitively establish the presence or absence of increased risks of stillbirth or neonatal deaths, low birth weight, preterm deliveries, NICU admissions, Apgar score lower than seven at five minutes, and neonatal jaundice following exposure to pivmecillinam during pregnancy or definitively confirm or refute the risk of childhood leukemia following in utero exposure to pivmecillinam.

No clinically significant differences in mecillinam C_{max} and AUC were observed in pregnant adult women (10 to 32 weeks gestation) administered PIVYA 185 mg orally in a published study.

Animal Data

Section [13.2](#) Individual Reviews of Studies Submitted With the New Drug Application contains the nonclinical information used to support labeling and the summaries of the reproductive-toxicology studies. Refer to [Table 57](#) for the reproductive and developmental safety margins. Developmental toxicity studies with pivmecillinam or MEC administered during organogenesis to rats and mice showed no evidence of embryo-fetal toxicity, including drug-induced fetal malformations, at doses approximately 3.4 or 7.9 times (rats) or 5.1 or 3.9 times (mice) higher than given to subjects receiving the maximum recommended daily dose (based on body surface area comparison). Evidence of slight fetotoxicity (reduced ossification) was seen in offspring of rats that were given pivmecillinam during organogenesis at a dose approximately 10.2-fold higher than the maximum recommended daily human dose (based on body surface area comparison). In pre and postnatal studies in rats where maternal animals were dosed beginning during gestation (Day 15) and continuing throughout the weaning period, neither pivmecillinam nor MEC had adverse effects on the maternal survival and development of the offspring. Pivmecillinam was given orally at doses up to 582 mg/kg/day and MEC was given subcutaneously at doses up to 450 mg/kg/day (approximately 10.2-fold and 7.9-fold higher than the maximum recommended daily human dose of PIVYA, based on body surface area, respectively).

MEC had no adverse effect on fertility in male or female rats at subcutaneous doses up to 450 mg/kg/day (approximately 7.9-fold higher than the maximum recommended daily human dose based on body surface area). Pivmecillinam had no adverse effect on fertility in male or female rats at oral doses up to 582 mg/kg/day (approximately 10.2-fold higher than the maximum recommended daily human dose based on body surface area). See [Table 57](#) for details.

Table 57. Reproductive and Developmental Toxicity Safety Margins

Study Type (Route of Administration)	NOAEL (mg/kg/day)	Safety Margin (Multiples)
Pivmecillinam		
Fertility rat (oral)	582	10.2
EFD rat (oral)	194	3.4
EFD mice (oral)	582	5.1
PPND rat (oral)	582	10.2
Mecillinam		
EFD rat (SC)	450	7.9
EFD mice (SC)	450	3.9
PPND rat (SC)	450	7.9

Source: Reviewer generated table based on reports provided by the Applicant.

Abbreviations: EFD, embryo-fetal development; NOAEL, no observed adverse effect level; PPND, pre-postnatal development; SC, subcutaneous injection

PK in Pregnant Women

While some differences in MEC pharmacokinetics were observed between pregnant and non-pregnant women administered IV MEC, these differences were minimal in pregnant subjects receiving oral pivmecillinam ([Heikkila 1993](#)). No dosage adjustments are recommended in pregnant women receiving pivmecillinam for UTIs.

Lactation

There are insufficient data on the presence of MEC in human milk. MEC is present in animal milk and may be present in human milk. In a study of lactating cows given 8 mg/kg MEC IV, the concentration in milk was 0.1 and 0.7 µg/mL at two and six hours, respectively, and the total excretion in milk over the first six hours was 0.03% of the injected dose. A PMR lactation study (milk only) will be conducted in lactating women who have received pivmecillinam to assess concentrations of pivmecillinam in breast milk using a validated assay and to assess the effects on the breastfed infant.

Interference with Newborn Screening Test

The Division of Pediatric and Maternal Health was consulted to assist with draft labeling for pediatric subjects, specifically regarding drug interference with the newborn screening test for isovaleric acidemia in the setting of in utero exposure and provided the following assessment and labeling recommendations. Refer to their review in DARRTS dated March 6, 2024.

Isovaleric acidemia (IVA) is a rare genetic condition which causes a deficiency of isovaleryl CoA dehydrogenase, which inhibits the proper breakdown of leucine containing proteins ([MedlinePlus 2020](#)) which leads to a buildup of isovalerylcarnitine, isovalerylglycine, isovaleric acid, and 3-hydroxyisovaleric acid ultimately causing metabolic ketoacidosis in those affected ([Murko et al. 2023](#)). Newborn screening for IVA is performed by mass spectrometry to quantify C5 carnitines. Isovalerylcarnitine is a C5 carnitine that accumulates in the blood of subjects with IVA; however, it is only one of several C5 carnitines that are detected as a group in this screening test. Pivaloylcarnitine, a metabolic product of pivmecillinam, is isomeric with isovalerylcarnitine and therefore contributes to the quantification of C5 carnitines, allowing for the possibility of a false positive result for this screening test for IVA ([Murko et al. 2023](#)).

When a positive screening test result is reported for IVA, several immediate actions are recommended, including contacting the caregiver and assessing the clinical status of the newborn. Symptomatic infants should be transported to the hospital immediately for treatment and consultation with a metabolic specialist. Confirmatory testing should be initiated which requires blood and urine samples be collected from the newborn.

In the setting of in utero exposure to pivmecillinam prior to delivery; if pivaloylcarnitine is determined to be the only elevated C5 carnitine and all other confirmatory tests are normal in an asymptomatic subject, then the screening test would be considered a false positive. The in-utero exposure may or may not be known prior to confirmatory testing; however, based on either the initial positive screening result or the results of confirmatory testing, the exposure can be investigated. Labeling changes were incorporated including the Warnings and Precautions section to alert HCPs that treatment of a pregnant woman prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of the NBS and that prompt follow up was recommended.

9. Product Quality

Approval With a Postmarketing Commitment

The Office of Pharmaceutical Quality (OPQ) review team has assessed NDA 216483 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this NDA from a quality perspective. From the biopharmaceutics perspective, limited information was provided in the NDA regarding the dissolution method development for the proposed commercial drug product. Therefore, the proposed dissolution method and acceptance criteria have been found acceptable on an interim basis with additional dissolution studies recommended to be performed via a postmarketing commitment (PMC). The CMC PMC agreement between OPQ and the Applicant is listed below (Section [24](#) Postmarketing Requirements and Commitments) and should be included in the action letter. For further details refer to the OPQ Review in DARRTS.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

The Applicant certified that following due diligence to locate clinical investigators who participating in the covered studies, there were no investigators identified with disclosable financial interests or arrangements; see Section [25](#) Financial Disclosure.

11. Advisory Committee Summary

Not applicable.

III. Additional Analyses and Information

12. Summary of Regulatory History

Pre-IND 118650 for pivmecillinam was submitted on May 24, 2013, by Leo Pharmaceutical Products Ltd. On February 12, 2018, the Division was informed that on February 01, 2018, ownership of PIND 118650, for pivmecillinam hydrochloride (HCL) tablets was transferred from Leo Pharmaceutical Products Ltd. to Utility Therapeutics Group Ltd. (Utility).

On May 04, 2018, Utility submitted to PIND 118650 a request for Qualified Infectious Disease Product (QIDP) designation under the GAIN Act for pivmecillinam HCL tablets for the indication of treatment of uncomplicated urinary tract infections (acute uncomplicated cystitis) in adult subjects, caused by the following susceptible microorganisms: *E. coli*, (b) (4), *Proteus spp.*, and (b) (4).

On June 29, 2018, the FDA granted QIDP designation to pivmecillinam HCL tablets for oral use for the treatment of uncomplicated urinary tract infections (uUTI).

On August 8, 2018, Utility submitted their IND application (IND 118650) for pivmecillinam HCL tablets for the proposed indications of uncomplicated urinary tract infections. The IND included a phase 1 protocol to study the safety, tolerability, and pharmacokinetics (PK) of pivmecillinam and mecillinam (MEC) in healthy adult subjects. On September 07, 2018, the IND was determined safe to proceed.

On October 31, 2018, a type B guidance meeting was held to discuss the nonclinical and clinical data package to support a future NDA submission for pivmecillinam HCL tablets for the treatment of uUTI. The Division provided recommendations on the information needed to support the preclinical, clinical pharmacology, and clinical data package for an NDA submission. The Division stated that to support clinical efficacy and safety, subject-level data from clinical studies would be necessary. During the meeting, the Division asked if Utility would consider conducting a randomized, controlled uUTI study. Utility replied they planned to rely on existing data.

On June 11, 2019, a type C guidance meeting was held to discuss whether the available efficacy and safety data are adequate to support an indication for treatment uUTI. During the meeting, the Division stated that Utility could focus on the proposed studies for primary efficacy analyses as long as Utility could provide a SAS database for subject level data. The Division asked Utility to review the proposed studies to determine if subject populations and test of cure assessments were comparable and if they met the inclusion criteria recommended in the FDA guidance document on uUTI ([August 2019](#)).

A type B preNDA meeting was held on April 6, 2021, wherein the planned NDA submission of pivmecillinam HCL tablets for the treatment of uUTI was discussed. The Division stated that the adequacy of using historical studies cannot be determined until the study data are fully reviewed under NDA. The Division continued to recommend that Utility conduct a prospective randomized study in uUTI. The Division acknowledged that reanalysis of efficacy studies to align with the current FDA uUTI guidance would improve the interpretation of the

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studies ([August 2019](#)). Utility stated that they would be providing genotoxicity study reports, sample datasets, and an initial Pediatric Study Plan in advance of the NDA submission.

On May 18, 2021, Utility submitted a request for review of the proposed proprietary name PIVYA. The name was found conditionally acceptable on November 10, 2021.

Utility submitted their initial Pediatric Study Plan, for the treatment of uUTI on September 22, 2021. The Division issued an iPSP agreement letter on February 25, 2022.

A pre-NDA meeting was scheduled for December 06, 2021, to discuss the format and content of the planned NDA submission for the treatment of uUTI. The Division issued preliminary comments on December 05, 2021, where the Division agreed with the general approach to the efficacy analysis. The Division recommended that an estimand framework according to the International Council for Harmonisation E9(R1) addendum ([November 2019](#)) be specified for each of the proposed primary efficacy studies, clearly indicating the treatment, population, variable of interest, intercurrent event handling, and summary measure for all estimands of interest (e.g., primary estimand, secondary and supportive estimands). It was also agreed that the NDA would be complete upon submission. Additionally, the Division recommended the Utility hold a Chemistry, Manufacturing and Controls pre-NDA meeting. After reviewing the comments Utility determined that no further discussion was needed.

On October 24, 2023, Utility Therapeutics Ltd. submitted NDA 216483 for pivmecillinam tablet for the treatment of adults with uUTI caused by susceptible (b) (4) and *S. saprophyticus*. The submission also included a request for the proprietary name PIVYA.

Utility was notified on December 22, 2023, that the application was sufficiently complete for the FDA to perform a substantive review and that the application received priority review designation with a PDUFA goal date of April 24, 2024. The NDA is a 505(b)(2) application.

On February 15, 2024, the proposed proprietary name, PIVYA, was determined to be conditionally acceptable.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

With the exception of the genetic toxicology study battery conducted on behalf of the current Applicant (necessary to write a label for an approved product according to current standards), the majority of the nonclinical studies conducted to support the approval of PIVYA were performed prior to the adoption of GLP regulations by (or on behalf of) the product originator, LEO Pharma A/S. There are also a few studies (not contemporary) conducted by (or on behalf of) Hoffman-LaRoche Inc (b) (4).

The Division agreed to accept these pre-GLP nonclinical studies in light of the previous favorable actions taken by FDA (b) (4), and because there is extensive clinical experience with these drugs.

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Additionally, it appears unlikely that repeating the nonclinical pharmacology/toxicology studies would provide additional relevant information important to the safety of PIVYA.

The body of data from the nonclinical studies conducted with pivmecillinam and MEC is summarized in Section [13.2](#) Individual Reviews of Studies Submitted With the New Drug Application.

Referenced NDAs, BLAs, DMFs

Many of the nonclinical studies used to support the current product were also submitted and reviewed under these NDAs:

- NDA 50565 (held by Hoffmann LaRoche Inc.) for MEC (trade name COACTIN, approved 1984) - withdrawn

(b) (4)

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Pharmacology

Primary Pharmacology

Pivmecillinam is a penicillin class antibacterial. Penicillins bind to the penicillin binding protein (PBP)-2 in gram-negative bacilli, inhibiting production of peptidoglycan and interfering with cell wall synthesis.

Secondary Pharmacology

In vitro receptor binding studies were not conducted with pivmecillinam or MEC.

Safety Pharmacology

Relevant safety pharmacology studies were not performed with orally administered pivmecillinam. The studies performed with parenterally administered pivmecillinam are not relevant because this is not the intended route of administration for this prodrug. Oral pivmecillinam doses of up to 200 mg/kg to cats (not a current standard species for safety pharmacology testing) had no effect on blood pressure, electrocardiogram, or heart rate. No changes in respiration, spinal reflexes, or EEG were observed in the cats.

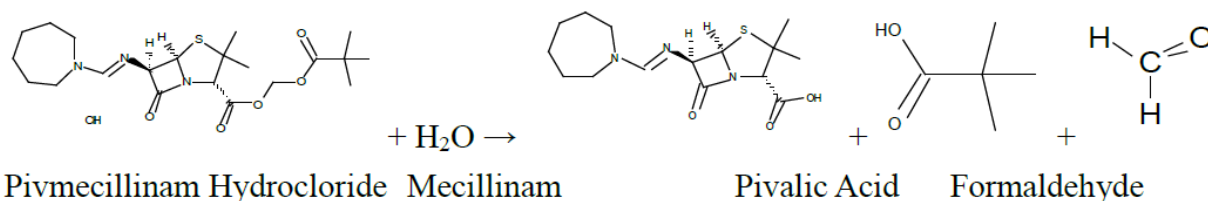
Intravenous doses of MEC up to 50 mg/kg in dogs did not affect arterial or venous blood pressure. In rats, a 20 mg/kg dose followed 30 minutes later by a 40 mg/kg dose was associated with a small, brief drop in blood pressure (20 mm Hg for 1 minute).

Absorption, Distribution, Metabolism, and Excretion/PK

At the time that the pivmecillinam and MEC nonclinical toxicology studies were conducted, toxicokinetic assessment was not usually included.

Upon absorption, pivmecillinam is rapidly converted to MEC by nonspecific plasma/tissue esterases as detailed in [Figure 1](#) (illustration from the nonclinical overview):

Figure 1. Conversion of Pivmecillinam to Mecillinam Upon Absorption



Source: Nonclinical Overview submitted by the Applicant

[Table 58](#), [Table 59](#), and [Table 60](#) from the PK Tabulated Summary in the NDA summarizes data from studies in rats and dogs conducted by LEO (TRA- total radioactivity; LSC- liquid scintillation counting):

Table 58. PK Tabulated Summary of Mecillinam Distribution in Dog (3F) and Rat (2F)

2.6.5.13A Pharmacokinetics: Excretion	Test Article: Pivmecillinam Hydrochloride					
Species	Rat ¹⁾			Dog ²⁾		
Gender (M/F)/Number of animals	2F			3F		
Feeding condition	Fasted			Fasted		
Vehicle/Formulation	Aqueous solution			Aqueous solution		
Method of Administration	Oral			Oral		
Dose (mg/kg)	20			30		
Analyte	TRA ^{a)}			TRA ^{a)}		
Assay	LSC			LSC		
Excretion route	Urine	Feces	Total	Urine	Feces	Total
Time						
0 – 2 hr	-	-	-	18.0		
2 – 4 hr	-	-	-	12.4		
0 – 6 hr	34.14	-	-			
4 – 8 hr	-	-	-	8.9		
6 – 12 hr	4.40	-	-			
8 – 24 hr	-	-	-	5.2		
12 – 24 hr	1.57	-	-			
0 – 24 hr	40.11	43.53	83.64	44.5	28.4	72.9
24 – 48 hr	0.66	4.65	5.31	2.0	15.4	17.4
48 – 72 hr	0.21	0.23	0.44	0.2	0.1	0.3
0 – 72 hr	40.98	48.41	89.39	46.7	43.9	90.6
Study number Location in CTD: 4.2.2.5	Andersen 1973b			Andersen 1973a		

Source: ([Roholt 1977](#)); A published review of PK studies in animals and humans conducted by Leo Pharmaceutical Products: Distribution of mecillinam in dogs (review article notes a similar pattern for both rats and rabbits)
Abbreviations: F, female; hr, hour; LSC, liquid scintillation counting; M, male; PK, pharmacokinetic; TRA, total radioactivity

Table 59. PK Tabulated Summary of Mecillinam Distribution in Dog (2F) and Rat (6F)

2.6.5.13C Pharmacokinetics: Excretion		Test Article: Mecillinam					
Species		<u>Rat</u>			<u>Dog</u>		
Gender (M/F)/Number of animals		6F			2F		
Feeding condition		Fasted			Fasted		
Vehicle/Formulation		Aqueous solution			Aqueous solution		
Method of Administration		Intravenous			Intravenous		
Dose (mg/kg)		15			20		
Analyte		TRA ^{a)}			TRA ^{a)}		
Assay		LSC			LSC		
Excretion route		Urine	Feces	Total	Urine	Feces	Total
Time							
0 – 2 hr		-	-	-	62.21	-	
2 – 4 hr		-	-	-	13.51	-	
0 – 6 hr		75.8	-	-	-	-	
4 – 8 hr		-	-	-	10.34	-	
6 – 24 hr		2.6	-	-	-	-	
8 – 24 hr		-	-	-	4.87	-	
12 – 24 hr		-	-	-	-	-	
0 – 24 hr		78.4	3.5	81.9	90.93	9.07	100
24 – 48 hr		0.9	10.3	11.2	0.46	0.95	1.41
48 – 72 hr		0.3	1.7	2.0	0.15	0.02	0.17
0 – 72 hr		79.6	15.5	95.1	91.54	10.04	101.58
Study number Location in CTD: 4.2.2.5		Andersen 1975			Andersen 1975		

Source: (Roholt 1977); A published review of PK studies in animals and humans conducted by Leo Pharmaceutical Products: Distribution of mecillinam in dogs (review article notes a similar pattern for both rats and rabbits)
Abbreviations: F, female; hr, hour; LSC, liquid scintillation counting; M, male; PK, pharmacokinetic; TRA, total radioactivity

Table 60. Serum and Organ Concentrations in the Dog 1 Hour After Intravenous Injection of Mecillinam 50 mg/kg Bodyweight

µg/ml Fluid or µg/g tissue (wet weight)					
Urine	20726	Ovaries	16	Adrenals	8·7
Bile	1475	Lymph node	14	Bone marrow	8·3
Kidneys	119	Spleen	12	Thymus	7·9
Liver	114	Pancreas	11	Eye	3·9
Serum	34	Heart	10	Medulla	1·4
Lungs	21	Muscle	10	Brain	0·6

Source: (Roholt 1977); A published review of PK studies in animals and humans conducted by Leo Pharmaceutical Products: Distribution of mecillinam in dogs (review article notes a similar pattern for both rats and rabbits)

This article also mentions data from studies in pregnant rats showing low fetal concentrations within half an hour of subcutaneous MEC administration (Roholt 1977). It also mentions data from a study in lactating cows where the animals were given 8 mg/kg of intravenous MEC to mimic serum concentrations found in treated humans. Milk concentrations were 0.1-0.7 µg/ml at timepoints taken two and six hours after injection, with total excretion in milk about 0.3% of the injected dose over six hours. However, there was no tabular data presented from the studies in pregnant rats or lactating cows.

Toxicology

Most of these studies were conducted prior to the adoption of GLP, with the exception of the genetic toxicology studies conducted on behalf of the current Applicant. The doses were expressed in terms of the salt (HCL), rather than free base. Toxicokinetic data were not collected at the time that the animal studies were performed.

General Toxicology

Pivmecillinam

Oral studies of 1 to 3 months duration were conducted in rats, dogs, and rhesus monkeys. Significant toxicity was not observed at the doses tested with the exception of dose-related vomiting in dogs and monkeys after administration and soft stool (with a few instances of diarrhea in high dose monkeys).

Rats were given up to 600 mg/kg (6 days/week) for 8 weeks (about 10-fold higher than the 600 mg daily recommended clinical dose based on body surface area), beagle dogs were given 200 mg/kg (6 days/week) for 47 days (about 11-fold higher than the clinical dose based on body surface area), and monkeys were given up to 630 mg/kg for 3 months (daily for first 4 weeks, 6 days/week for remainder with the high dose divided to improve gastric tolerance) (about 20-fold higher than the clinical dose based on body surface area). Some additional findings in the monkey study were slightly increase liver weight in high dose males (no histopathologic correlate), moderate increase in smooth endoplasmic reticulum in the convoluted tubular epithelium of the kidney (high dose both sexes), increased fat staining in renal medulla (high dose females only). There were no degenerative changes associated with the kidney findings and they may have been adaptive due to the high renal excretion of this drug. The no observed adverse effect level (NOAEL) in the monkey study was the mid dose of 210 mg/kg (except some occasions of vomiting/soft stool) (about 6.8-fold higher than the clinical dose based on body surface area). The NOAEL in the rat study was the high dose of 600 mg/kg. Except for the occasional vomiting, the NOAEL in the dog study was 200 mg/kg.

Longer term studies were also conducted but may be less relevant considering the short-term clinical use of PIVYA. Nonetheless, the data from these studies are reassuring in terms of safety, as the NOAELs for pivmecillinam in both rats and dogs provided an approximate four-fold margin of safety compared to the daily clinical dose and most findings were at doses that exceed the clinical dose by a higher margin.

A 26-week oral study of pivmecillinam in rats had a NOAEL of 210 mg/kg/day (the mid dose, about 3.7-fold higher than the clinical dose based on body surface area). At 630 mg/kg/day, reduced body weight gain and increased absolute weight of the liver and kidneys were observed, but there were no histopathological findings or treatment-related changes in hematology, clinical chemistry, and urinalysis.

A 26-week oral pivmecillinam study in beagle dogs had a NOAEL of 70 mg/kg/day (the low dose, about 3.8-fold higher than the clinical dose based on body surface area), excepting occasional instances of vomiting. Dose-related vomiting was observed in all groups (70, 210, and 630 mg/kg/day). The high dose was divided into two daily doses to improve gastrointestinal tolerance. Dose-related reductions in RBC values associated with mild anemia were observed at the mid and high doses by the end of the study. Additional findings at the high dose included

increases in ALP, urea, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), some of which were transient over the course of the study or present in individuals within the high dose group. One animal in the high dose group was sacrificed in poor condition. The high dose dogs did not gain weight at the same rate as the other groups (treated and control), and this was associated with reduced food consumption. All of the dogs in the high dose group had enlarged livers at necropsy. The pathologist noted “slight degenerative cell changes” in the livers of 2/6 mid dose dogs (1 male, 1 female). More prominent changes were observed in the high dose dogs with hepatocytes said to have “distended” cytoplasmic content with vacuolation. The high dose males also had fatty infiltration in the peripheral zone of all liver lobules (the male that was sacrifice early was said to have a more diffuse fatty infiltration of the liver). The pathologist noted that neither necrotic nor inflammatory changes were observed in the liver. The kidneys of high dose dogs had a more prominent fat staining compared to controls or the other treatment groups, along with renal tubular vacuolation. The pathologist noted that there were no necrotic or inflammatory changes in the kidneys. An additional 26-week study was conducted in beagle dogs to determine whether liver findings were reversible. Dogs received 315 mg/kg twice daily for 14 weeks (630 mg/kg/day). Liver biopsies were taken at Week 12 of dosing, at the end of dosing, and at Weeks 3, 5, 8, and 25 (necropsy) of the recovery period. Blood samples for clinical chemistry were taken during Weeks 4, 8, 12, and 14 of dosing and Weeks 2, 4, 7, 24, and 25 of recovery. No changes in plasma urea or ALP were observed. ALT and AST were elevated at the end of dosing in several animals but had returned to normal by two weeks after dosing. Liver biopsies showed hepatocyte enlargement, deposition of basophilic pigment in Kupfer cells and sinusoids, and intracytoplasmic eosinophilic granules in all dogs, and intracytoplasmic basophilic granules in two out of four dogs. However, fat infiltration was not observed in the liver of any animal during this second/recovery study. During the recovery period, hepatocytes returned to normal size, intracytoplasmic eosinophilic granules disappeared, and basophilic pigment was present in a trace amount in only one out of four dogs and no longer present in the others by Week 25. Basophilic granules persisted in the hepatocyte cytoplasm in three out of four dogs, but it was significantly reduced in two. The hepatocyte cytoplasm of the dog with the persistent basophilic granules had a ground glass appearance. In neither the 26-week study nor the 14-week (plus recovery) study were necrotic or inflammatory changes observed in the liver of any dog.

Mecillinam

In beagle dogs, intravenous bolus doses of MEC at 500 mg/kg administered over 3 minutes caused vomiting, shivering, increased pulse rate, and prostration. Mortality did not occur and the dogs appeared normal within 1 to 2 hours. This dose was given daily for 22 days and these reactions became less severe over the course of the study. Treatment-related body weight changes were not observed and hematology parameters remained in the normal range, though slightly reduced compared with predose levels. ALT fell approximately 60 to 75% during the first week of the study and remained at that level for the duration of the study. ALP rose slightly over the course of the study. According to the report, there were no microscopic changes related to MEC, but it did not contain specific information as to which tissues were evaluated.

A 13-week study of MEC in beagle dogs used subcutaneous administration. The NOAEL in this study was 50 mg/kg/day (about 2.7-fold higher than the clinical dose). Reduced food consumption and body weight gain were observed at the high dose, 450 mg/kg/day. Increased

ALP and increased mean liver weights were also seen at the high dose. Microscopic evaluation revealed enlarged hepatocytes with intracytoplasmic basophilic and/or eosinophilic granules and minimal to mild deposition of basophilic pigment in Kupfer cells in all high dose dogs. Hepatocyte enlargement and/or basophilic pigment deposition were also observed in one to two (out of six total) animals that received the mid dose of 150 mg/kg/day. There were no liver changes indicative of hepatocellular necrosis or degeneration in any dog. No treatment-related findings were observed in the kidneys or any of the other tissues examined. An additional subcutaneous administration study was conducted with MEC in beagle dogs to assess reversibility of the liver findings (similar to the pivmecillinam reversibility study described above). In the reversibility study, the dogs received 450 mg/kg/day for 14 weeks followed by a 25-week recovery period. Liver biopsies were taken prior to the initiation of dosing, at Week 12 of dosing, at the end of dosing, during the recovery period (exact times not specified) and samples for microscopic evaluation were also taken at necropsy. Blood samples for clinical chemistry (urea, ALP, AST, ALP) were taken during Weeks 4, 8, 12, and 14 of dosing and Weeks 2, 4, 7, 24, and 25 of recovery. During the dosing period, all MEC-treated dogs developed the liver changes (hepatocyte enlargement, basophilic pigment deposition in sinusoids and/or Kupfer cells, intracytoplasmic eosinophilic globules and basophilic granules in hepatocytes) that were seen during the initial MEC dog study. During the drug-free observation/recovery period, complete reversal of hepatocyte enlargement occurred, and eosinophilic granules were no longer present. Liver weights were within the normal range by the end of recovery. The deposition of basophilic pigment and basophilic granules persisted. Plasma urea and AST remained within the normal range during this study. ALP increased during the dosing period in all animals, but returned to normal range within weeks of recovery. ALT was elevated in one dog by the end of dosing but returned to normal range within 2 weeks of recovery. There were no signs that any liver changes became worse after dosing ended, and most showed signs of reversibility during the recovery period (excepting persistence of basophilic material).

A 13-week study with MEC was also conducted in rats, using the subcutaneous route of administration at doses of 50, 150, and 450 mg/kg/day. A conservative NOAEL would be the low dose of 50 mg/kg/day (about 0.8-fold the daily clinical dose based on body surface area), due to the increased liver weight seen at the mid dose, but as there was no histopathologic correlate at the mid dose, one might argue that it could be considered the NOAEL. Clinical signs of toxicity and changes in body weight gain were not observed in the rats treated with MEC, and there were no treatment-related changes in hematology, serum chemistry, or urinalysis parameters. Dose-related increases in mean absolute and relative liver weights were observed at necropsy at the mid and high dose, but the only histopathologic correlate was hepatocyte enlargement with increased cytoplasmic vacuolation at the high dose. A small increase in relative kidney weight was observed at the high dose, but there was no histopathologic correlate.

Pivalic Acid

Pivalic acid was not toxic to rats or mice at oral doses up to 120 mg/kg/day (highest dose tested) for 1 month. However, treatment with pivalic acid prodrugs has been reported to cause carnitine deficiency in humans (pivalic acid is excreted into the urine as a conjugate with L-carnitine in humans and cynomolgus monkeys). The risk of carnitine deficiency is increased with a longer duration of dosing.

Genetic Toxicology

The studies below show that MEC is neither mutagenic nor clastogenic in a standard battery of genetic toxicity tests. Because cytotoxicity limited evaluation of MEC in two bacterial strains used in the Ames test, (Q)SAR evaluation was performed by the CDER Computational Toxicology Consultation Service to confirm that MEC would be predicted to be negative for bacterial mutagenicity. Pivmecillinam was negative in an in vivo mouse bone marrow micronucleus test, but it was mutagenic in the Ames assay and clastogenic in cultured human lymphocytes. This is considered due to the release of formaldehyde from the prodrug linker. Formaldehyde is known to be genotoxic. Although it is rapidly eliminated in vivo, formaldehyde is likely to be present for a longer time in vitro.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study Title/Number: Mecillinam - Bacterial Reverse Mutation Test/Study No. 47891 MMO

Key Study Findings:

- MEC was not mutagenic.

GLP compliance: Yes

Test system: *S. typhimurium* TA 98, TA 100, TA 102, TA 1535, TA 1537, $\pm$ rat liver S-9

Study is valid: Yes, but evaluation of TA 1535 and TA 1537 was limited by cytotoxicity.

Study Title/Number: Pivmecillinam Hydrochloride EP - Bacterial Reverse Mutation Test/Study No. 47896 MMO

Key Study Findings:

- Pivmecillinam was mutagenic in the presence of metabolic activation (rat liver S-9).

GLP compliance: Yes

Test system: *S. typhimurium* TA 98, TA 100, TA 102, TA 1535, TA 1537, $\pm$ rat liver S-9

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study Title/Number: Mecillinam - In Vitro Micronucleus Test in Cultured Human Lymphocytes/Study No. 47892 MNH

Key Study Findings:

- MEC did not induce chromosome damage or damage to the cell division apparatus.

GLP compliance: Yes

Test system: Primary cell cultures of human lymphocytes from female blood donors (nonsmokers and no recent radiography) stimulated with PHA, $\pm$ rat liver S-9

Study is valid: Yes

NDA 216483
PIVYA (pivmecillinam)

Study Title/Number: Pivmecillinam Hydrochloride EP - In Vitro Micronucleus Test in Cultured Human Lymphocytes/Study No. 47897 MNH

Key Study Findings:

- Pivmecillinam induced chromosome damage or damage to the cell division apparatus, in cultured human lymphocytes when treated for 24 hours in the absence of metabolic activation (S-9).

GLP compliance: Yes

Test system: Primary cell cultures of human lymphocytes from female blood donors (nonsmokers and no recent radiography) stimulated with PHA, $\pm$ rat liver S-9

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study Title/Number: Mecillinam-Bone Marrow Micronucleus Test by Intravenous Route in Mice/Study No. 47893 MAS

Key Study Findings:

- MEC was not clastogenic following 2 daily intravenous doses up to 300 mg/kg/day.

GLP compliance: Yes

Test system: Swiss mice, Crl:OF1

Study is valid: Yes

Study Title/ Number: Pivmecillinam Hydrochloride EP - Bone Marrow Micronucleus Test by Oral Route in Mice/Study No. 47898 MNH

Key Study Findings:

- Pivmecillinam was not clastogenic following 2 daily oral doses up to 2000 mg/kg/day.

GLP compliance: Yes

Test system: Swiss mice, Crl:OF1

Study is valid: Yes

Carcinogenicity

Not conducted with either pivmecillinam or MEC. Not needed for this product.

Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Pivmecillinam

The NOAEL for fertility in rats was the high pivmecillinam dose of 630 mg/kg/day (about 11-fold higher than the clinical dose). Wistar rats were treated with pivmecillinam at oral

doses of 0 (distilled water vehicle control), 210, and 630 mg/kg/day beginning 70 days prior to mating for males and 20 days prior to mating for females (1:2 male to female mating within same dose group). Dosing continued until scheduled sacrifice (10 females were sacrificed on gestation day (GD) 15 and 20 were allowed to litter, with parturition observed directly when possible). Slight reduction in body weight gain at the high dose was the only adverse clinical effect seen in the parental animals, except that the test solution was irritating to the esophagus and stomach and contributed to some dosing errors. Pivmecillinam treatment did not affect mating performance or pregnancy rate, and the gestation period was also comparable between drug treated and control groups. Drug treatment did not appear to adversely affect pre or postimplantation loss. Litter size and pup mortality was comparable between control and treated groups at birth and throughout lactation until weaning. Pup weight was slightly higher in the pivmecillinam groups compared to control. No drug-related abnormalities were observed in the pups. Sperm parameters were not evaluated in this study (not expected in a study conducted in 1973).

Mecillinam

The NOAEL for fertility in rats was the high MEC dose of 450 mg/kg/day (about 7.9-fold higher than the clinical dose). Wistar rats received MEC subcutaneously at doses of 0 (0.9% saline control), 150, and 450 mg/kg/day beginning 64 days prior to mating for males and 2 weeks prior to mating for females (1:2 male to female mating within same dose group). Dosing continued until scheduled sacrifice (approximately half of the females were sacrificed on GD 13 and the other half were allowed to litter, with parturition observed directly when possible). No signs of clinical toxicity were observed in the drug-treated animals except that drug-treated males gained slightly less weight than controls. Females in all groups gained similar amounts of weight during pregnancy. No differences in mating performance were observed and the gestation period was comparable between control and treated groups. Litter size, pup weights, and pup mortality were comparable between groups. Sperm parameters were not evaluated in this study (not expected in a study conducted in 1974).

A two-generation study was conducted with MEC where F0 parental animals were dosed beginning prior to conception and selected F1 offspring were observed during the postnatal period and mated to determine their fertility. Consistent with the fertility study above, the NOAEL was 450 mg/kg/day. Wistar rats received MEC subcutaneously at doses of 0 (vehicle control), 50, 150, and 450 mg/kg/day beginning 9 weeks prior to mating for males and beginning 2 weeks prior to mating for females (1:2 male to female mating within same dose group). Dosing continued until scheduled sacrifice (approximately half of the females were sacrificed on GD 21 and the other half were allowed to litter). One male and one female pup from each litter (F1) were selected for postlactational observation and breeding. Their offspring (F2) were observed until weaning, when they were sacrificed. Body weight gain was similar between F0 parental animals in the control and drug-treated groups and no clinical signs of toxicity were noted. F0 mating performance and pregnancy rate were not affected by treatment and the gestation period was also comparable between groups. Although mean litter size at birth in the high dose group was less than control (8.4 versus 10.5 pups), the difference was not observed in the animals that were sacrificed on GD 21. The difference did not appear to be due to resorption, and no effect on peri/neonatal or postnatal viability was observed between the control and treated groups, including the high dose. The F1 generation from drug-treated parents developed similarly to

controls in terms of body weight gain, general appearance, and behavioral, auditory, or visual observations. The animals from the F1 groups that were chosen for mating did not show any drug-related differences in fertility (mating, pregnancy rate, and gestation period were comparable) and the F2 offspring did not show any signs of toxicity or changes in their postnatal development. No drug-related abnormalities were observed in the F1 or F2 pups. Sperm parameters were not evaluated in this study (not expected in a study conducted in 1976).

Embryo-Fetal Development

Pivmecillinam

The NOAEL for pivmecillinam developmental toxicity in rats in this study was the mid dose of 210 mg/kg/day (about 3.7-fold higher than the clinical dose based on body surface area). Pregnant Wistar rats were given pivmecillinam at oral doses of 0 (distilled water vehicle control), 70, 210, and 630 mg/kg/day on GD 6 to 15. Dams were sacrificed on GD 21. There were no clinical signs of maternal toxicity, and body weight gain in the treated dams did not differ significantly from controls. Litter parameters (size, pre or postimplantation loss) did not differ between groups and mean pup weights were also similar. There were no treatment-related changes in the incidence of malformations observed in the offspring up to the highest dose tested, but at the highest dose group, 630 mg/kg/day, reduced ossification of sternebrae was observed. This may indicate a slight fetotoxicity of pivmecillinam at this dose (about 11-fold higher than the clinical dose).

The NOAEL for pivmecillinam developmental toxicity in mice in this study was 630 mg/kg/day (about 5.5-fold higher than the clinical dose based on body surface area), the highest dose tested. Pregnant NMRI mice were given pivmecillinam at oral doses of 0 (distilled water vehicle control), 70, 210, and 630 mg/kg/day on GD 6 to 15. Dams were sacrificed on GD 17. There were no clinical signs of maternal toxicity, and body weight gain in the treated dams did not differ significantly from controls. Litter parameters (size, pre or postimplantation loss) did not differ between groups and mean pup weights were also similar. There were no treatment-related changes in the incidence of malformations observed in the offspring.

Mecillinam

The NOAEL for MEC developmental toxicity in rats in this study was 550 mg/kg/day (about 8.8-fold higher than the clinical dose based on body surface area), the highest dose tested. Pregnant Wistar rats were given MEC subcutaneously at doses of 0 (phosphate buffer vehicle control), 60, 185, and 550 mg/kg/day on GD 6 to 15. Dams were sacrificed on GD 21. There were no clinical signs of maternal toxicity, and body weight gain in the treated dams did not differ significantly from controls. Litter parameters (size, pre or postimplantation loss) did not differ between groups. Mean pup weights were slightly higher in the high dose group compared to control. There were no treatment-related changes in the incidence of malformations observed in the offspring.

The NOAEL for MEC developmental toxicity in mice in this study was 550 mg/kg/day (about 4.4-fold higher than the clinical dose based on body surface area), the highest dose tested. Pregnant Crl:CD mice were given MEC subcutaneously at doses of 0 (phosphate buffer vehicle control), 60, 185, and 550 mg/kg/day on GD 6 to 15. Dams were sacrificed on GD 17. There were no clinical signs of maternal toxicity, and body weight gain in the treated dams did not

differ significantly from controls. Litter parameters (size, pre or postimplantation loss) did not differ between groups. Mean pup weights were similar in the drug-treated groups compared to control. There were no treatment-related changes in the incidence of malformations observed in the offspring.

Prenatal and Postnatal Development

In addition to the two-generation rat study described above that provided some information regarding pre and postnatal development of offspring of parental animals that received MEC, specific pre and postnatal studies were conducted with pivmecillinam and MEC.

Pivmecillinam

The NOAEL for pivmecillinam on pre- and postnatal development was 630 mg/kg/day (about 11-fold higher than the clinical dose based on body surface area), the highest dose tested. Pregnant Crl:CD rats (20/dose group) received oral pivmecillinam at doses of 0 (distilled water vehicle control), 70, 210, and 630 mg/kg/day on GD 15 through lactation day (LD) 21. All dams were allowed to deliver and care for their offspring before they were all sacrificed on LD 21. All pups were examined for external abnormalities and had their sex confirmed at sacrifice and about one third of each litter underwent necropsy with internal gross evaluation and weights of heart, liver, and kidneys recorded. The dosing solution used for the high dose was irritating and associated with some dosing errors (mortality in two dams and several instances of prolonged respiratory distress in three others). One of the dams that experienced more instances of respiratory distress in this group had a litter of dead pups and another cannibalized its litter before the end of LD 1. The pups in these two litters were grossly underweight. Considering that the remaining litters in this group did not show signs of toxicity in dams or offspring, the findings in the dams that experienced repeated respiratory distress was considered procedure-related rather than related to pivmecillinam exposure. Body weight gain during pregnancy was similar between control and pivmecillinam-treated groups if the dams with respiratory distress are excluded from the high dose group. Body weight gain during pregnancy was slightly reduced at the high dose if these dams are included, but it seems appropriate to exclude the animals that experienced periods of prolonged respiratory distress, and their offspring, from evaluation. Maternal body weight during the lactation period was similar between all dose groups. The number of implantation sites per dam, average litter size at birth, and average postimplantation loss did not differ between control and pivmecillinam-treated groups. Excluding the pups from the high dose group from the dams that experienced procedure-related respiratory distress, pup weights on LD 4 and LD 21 did not differ between control and pivmecillinam-treated groups, nor did viability or lactation indices. Sex ratio at weaning was within normal range for all groups and examination and necropsy of the pups did not reveal any drug-related differences in organ weights or abnormalities.

Mecillinam

The NOAEL for MEC on pre- and postnatal development was 450 mg/kg/day (about 7.9-fold higher than the clinical dose based on body surface area), the highest dose tested. Pregnant Crl:CD rats (20/dose group) received MEC by subcutaneous injection at doses of 0 (0.9% saline vehicle control), 60, 150, and 450 mg/kg/day on GD 15 through LD 21. All dams were allowed to deliver and care for their offspring before they were all sacrificed on LD 21. All pups were

examined for external abnormalities and had their sex confirmed at sacrifice and about one third of each litter underwent necropsy with internal gross evaluation and weights of heart, liver, and kidneys recorded. Skin lesions were observed at the injection sites of high and mid dose dams (dose-related), and could have been due to the irritating nature of the test article or high osmolality of the injection solution. No signs of systemic toxicity were observed in the dams and treatment with MEC did not suppress body weight gain in the dams during pregnancy or lactation. Litter size at birth, mean number of implants, and postimplantation loss were similar between control and MEC-treated groups. There did not appear to be any drug-related effect on the length of gestation, gestation index, or birth index. Pup survival, weight at birth and weight gain throughout lactation did not differ between the control and MEC-treated groups. Neonatal viability and lactation index were also unaffected by drug treatment. Sex ratio at weaning was within normal range for all groups and examination and necropsy of the pups did not reveal any drug-related differences in organ weights or abnormalities.

14. Clinical Pharmacology

14.1. In Vitro Studies

14.1.1. Plasma Protein Binding

The Applicant has submitted three studies that evaluated MEC (the active antibacterial moiety of pivmecillinam HCL [PIV]) plasma protein binding (PPB) in human plasma (Studies: ADM-19-2734, [Tybring 1975](#), Sadek 1977). The study by Sadek 1977 was not reviewed as the study's objective was to evaluate the stability of plasma proteins in the presence of MEC using a turbidity measurement via normal light transmission methodology, which is not considered appropriate to determine PPB by the review team.

Study ADM-19-2734 included the evaluation of free fraction using 1 μ M (0.33 μ g/mL) MEC in human plasma. The study findings suggested no PPB with free fraction measured as 101% (N=3) by Rapid Equilibrium Dialysis (RED) method followed by analysis with UPLC-MS/MS. MEC plasma concentrations of 1 μ M is clinically relevant as on average concentrations up to 1.7 μ g/mL are anticipated with the proposed dosing regimen of 200 mg PIV three times daily.

Tybring 1975 reported the free fraction of MEC (concentration not reported) in human serum as approximately 95 to 90%, which was evaluated by ultrafiltration method followed by quantification by bioassay ([Tybring 1975](#)).

An additional publicly available report on MEC PPB was found by the review team ([Reeves et al. 1975](#)). The free fraction of MEC (at 10 μ g/mL) in human serum was reported between approximately 75 to 85% by ultrafiltration and ultracentrifugation methods followed by quantification by bioassay.

Overall, the review team concludes that MEC has low plasma protein binding, however, the specific degree of PPB is unclear due to limited details available on the MEC concentrations studied. The Applicant's proposed labeling language is: "Mecillinam binds minimally to plasma proteins (5-10%)". Considering the limitations noted above, the Review team recommends

modifying the statement to say, “The degree to which mecillinam binds to plasma proteins is <25%.”

14.1.2. Drug Metabolism

The metabolism of PIV was investigated in human whole-blood ([Roholt et al. 1975](#)). The literature reports that after addition of 14.6 µg/mL PIV to human heparinized whole-blood at pH 7.4 and 37°C, its half-life was approximately 10 minutes. The same report noted that following oral administration of 500 mg PIV in six healthy subjects, negligible amounts (<0.02 µg/mL) of PIV was detected in the blood starting as early as 5 minutes postdose and persisting through four hours. The authors noted that nonspecific esterases in tissue and blood are responsible for PIV’s hydrolysis and postulated that subsequently pivalic acid is split off enzymatically with formation of the unstable hydroxymethyl ester of MEC which subsequently decomposes spontaneously into MEC and formaldehyde. The metabolism of PIV was also investigated in human liver microsomes (Study ADM-19-2734a). PIV’s estimated half-life and hepatic extraction ratio were 1.47 minutes and 97%, respectively. Thus, PIV has no or low potential to be a cytochrome P450 enzyme (CYP) substrate.

The metabolism of MEC was investigated in human liver microsomes (Study ADM-19-2734a). MEC was relatively stable with a predicted half-life and hepatic extraction ratio of 193 minutes and 22%, respectively. This finding is in line with the mean percentage of the dose excreted unchanged in the urine observed in Heikkilä et al. 1992 (See Section [14.2.3](#)) ([Heikkilä et al. 1992](#)).

14.1.3. CYP Enzyme-Mediated Drug-Drug Interactions

The Applicant conducted in vitro enzyme-mediated drug-drug interaction (DDI) studies to evaluate CYP inhibition and induction potentials of MEC (Study ADM-19-2734). Utilizing the study findings and thresholds noted in FDA’s guidance for industry *In Vitro Drug Interaction Studies Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* ([January 2020](#)), MEC’s potential as either a victim or perpetrator of significant clinical DDIs was evaluated.

MEC inhibition potential was evaluated with pooled human liver microsomes over a MEC concentration range from 0.2 to 150µM. MEC showed no or low potential as a direct inhibitor of CYP 1A2, 2B6, 2C9, 2C19, or 2D6 (half maximal inhibitory concentration [IC₅₀] >150µM versus predicted unbound maximum plasma concentration (C_{max}) = 3.4µM). The findings showed MEC has no or low potential for time-dependent CYP inhibition.

MEC induction potential toward CYP1A2, 2B6, and 3A4 was evaluated with human donor hepatocyte cultures over a MEC concentration range from 1-150µM. The findings showed MEC has no or low potential for CYP450 induction (induction fold change <2).

Model assumptions for predicting DDI potential were as follows:

1. Dose 200 mg PIV;
2. MEC C_{max} = 1.7 µg/mL or 3.9µM;
3. $f_{u,p}$ = 0.10 based on in vitro data, worst case; and
4. Nominal in vitro drug concentrations (e.g., IC₅₀).

Refer to the FDA guidance document on In Vitro DDI ([January 2020](#)) for all equations and other default parameter specifics.

14.1.4. Transporter-Mediated Drug-Drug Interactions

The Applicant conducted in vitro transporter-mediated DDI studies to evaluate MEC's potential as hepatic and renal transporter substrate and inhibitor (Utility-01-23 August 2018).

Substrate potential: Studies evaluated BCRP, PgP, MATE1, MATE2-K, OAT1, OAT3, OATP1 B1/B3 and OCT2 mediated transport of MEC (Concentrations: 1, 10, 100, and 300 μ M) in overexpressing cell culture monolayers or membrane vesicles. While 4 concentrations were evaluated, results for 1 μ M and 10 μ M were not interpretable due to the lower limit of quantification. The study findings with 100 μ M and 300 μ M showed MEC is a substrate of MATE1, MATE2-K, and OAT3 drug transporters (net flux ratio >2) (See [Table 61](#)). Publicly available clinical studies were submitted by the Applicant to further evaluate MEC as substrate of OAT3 transporter (See Section [14.2.6](#)). Because no clinical study was conducted for MATE1 and MATE2-K inhibitors, drug labeling language will be added that is similar to the OAT3 inhibitor language.

Inhibition potential: Studies evaluated BCRP, PgP, MATE1, MATE2-K, OAT1, OAT3, OATP1 B1/B3 and OCT2 transporter inhibition by MEC (Concentration range: 1.37 μ M -1000 μ M) in overexpressing cell culture monolayers or membrane vesicles. Utilizing the study findings and thresholds noted in the FDA guidance document on In Vitro DDI ([January 2020](#)), MEC's potential as either a victim or perpetrator of potentially significant clinical DDIs was evaluated (See [Table 61](#)).

Overall, the study findings (See [Table 61](#)) showed MEC has no inhibition potential for BCRP, PgP, MATE2-K, OAT1, OATP1 B1/B3, and OCT2 drug transporters. MEC showed low inhibition potential for MATE1 and OAT3 drug transporters with maximum inhibition of 59% and 70%, respectively. Based on the estimated IC₅₀ values, the in vivo DDI potential of MEC as MATE1 or OAT3 inhibitor is low ([Table 61](#)).

Model assumptions for predicting DDI potential were as follows: (i) dose 200 mg PIV; (ii) MEC C_{max} = 1.7 μ g/mL or 1.39 μ M; (iii) $f_{u,p}$ = 0.10 based on in vitro data, worst case; (iv) nominal in vitro drug concentrations (e.g., IC₅₀). Refer to the FDA guidance document on In Vitro DDI ([January 2020](#)) for all equations and other default parameter specifics.

Table 61. In Vitro Assessment of MEC as Substrate or Inhibitor of Human Uptake and Efflux Transporters

Transporter	In Vitro Findings ^a		In Vivo Potential Predictions ^b		Clinical Study Data Available
	Max Flux Rate Ratio	IC ₅₀ (μM)	Basic Model Predictions (Reviewer Analysis)	Interpretation (Substrate/Inhibitor)	
BCRP	1.18	>300	$I_1^c / IC_{50} < 0.1$	---	
P-gp	1.70	>300	$I_1^c / IC_{50} < 0.1$	---	
OATP1B1	0.83	>1,000	$R < 1.1$	---	
OATP1B3	1.65	>1,000	$R < 1.1$	---	
OAT1	1.92	>1,000	$I_{max, u} / IC_{50} < 0.1$	---	
OAT3	28.11	399	$ER > 2$ $I_{max, u} / IC_{50} < 0.1$	Substrate	Yes, Clinical DDI data available with probenecid.
OCT2	1.93	>1,000	$I_{max, u} / IC_{50} < 0.1$	---	
MATE1	2.3	672	$ER > 2$ $I_{max, u} / IC_{50} < 0.1$	Substrate	No
MATE2K	2.3	>1,000	$ER > 2$ $I_{max, u} / IC_{50} < 0.1$	Substrate	No

Source: Utility-01-23 Aug 2018 and information compiled by the Reviewer.

^a Assay solubility limit of 1,000μM (inhibition studies) or 300μM (substrate studies)

^b Predictions based on equations and thresholds specified in the 2020 FDA In Vitro DDI Guidance document.

^c $[I_1]$ = Total MEC C_{max} = 1.7 μg/mL or 1.39μM

^d $[I]_{max}$ = 1.3 μg/mL or 3.9μM; estimated max plasma concentration of inhibitor at the inlet to the liver.

Abbreviations: (---), not significant; DDI, drug-drug interaction; ER, efflux ratio; IC₅₀, half-maximal inhibitory concentration; $I_{max, u}$, maximum unbound plasma concentration of interacting drug at steady-state; MEC, mecillinam; R, ratio using basic model of reversible inhibition in liver and $[I]_{in, max}$

14.2. In Vivo Studies

14.2.1. Mouse Pharmacokinetics and Pharmacodynamics

MEC demonstrated activity in two animal models of infection relevant to the uncomplicated urinary tract infection indication. Briefly, while the study findings are summarized below, reliance on these findings was limited to supporting the review of Section 12.2 Pharmacodynamics language of the Prescribing Information proposed by the Applicant.

The rationale for this limitation was that while nonclinical data are positive, it remains to be established within the scientific community, how to generate robust and informative nonclinical PK/pharmacodynamic (PD) data from uncomplicated urinary tract infection models as well as what considerations are important during translating nonclinical urinary PK/PD evaluations into clinical efficacy predictions.

We recognize FDA's guidance document on uUTI ([August 2019](#)) states urinary concentrations of the drug are important when bacterial infection is limited to the lower urinary tract. Thus, urine specific PK/PD parameters are expected to inform efficacy evaluation for uUTI. However, there are still significant knowledge gaps in terms of urine-specific PK/PD parameter standards and quantitative association between nonclinical urinary PK/PD evaluations and clinical response/outcome. The Applicant has not provided data/evidence to fill these existing knowledge gaps. Thus, the translational utility of the provided nonclinical PK/PD data is limited, currently.

Mouse Neutropenic Thigh Infection Model

- The in vivo PD activities of MEC were characterized in a mouse neutropenic thigh infection model against 4 clinical *E. coli* strains (minimum inhibitory concentration [MIC] range: 0.38 to 16 mg/L; including 1 susceptible strain producing the carbapenemase NDM-1, and one resistant ESBL producing strain) (Jacqueline, 2022). A single 200 mg/kg MEC dose was administered subcutaneously (SC) 2 hr post bacterial inoculation (approximately 10^6 to 10^7 colony-forming unit [CFU]/ml). Activity was measured based on thigh bacterial counts (CFU/mL) measured at 24 hours post-inoculation (n=3/group). MEC PK was characterized following a single SC 200 mg/kg dose in a separate cohort by serum sampling via cardiac puncture at 0.25 to 6 hr (n=3/time point) after dosing. Infection status for the PK cohort is unclear. Like other penicillins, fraction of time (%) of the dosing interval for which free drug concentrations exceed the MIC ($\%fT_{C>MIC}/\tau$) was the PK/PD index correlating with antibacterial activity. Median plasma PK/PD target of 25% (range: 20.7 to 50.7) was associated with net-bacterial stasis in thigh. Net stasis was achieved against all tested isolates with the ESBL producing strain resulting in the higher 50.7% target. Median plasma PK/PD target of 81.1% (range: Not Achieved to 88.9) was associated with 1-log₁₀ bacterial reduction in thigh. One-log₁₀ bacterial kill was achieved in an OXA-48 producing strain and an ESBL producing strain but not achieved in an NDM-1 producing strain and a different ESBL producing strain.

Mouse Urinary Tract Infection Model

- An investigation on MEC PK/PD indices and targets was evaluated in a murine urinary tract infection (UTI) induced via urethral catheterization with an ESBL-producing *E. coli* (CTX-M9, MIC= 0.5 mg/L) (Vingsbo Lundberg C et al. 2009). The relationship between bacterial reduction and PK/PD parameters suggests that $\%fT_{C>MIC}/\tau$ correlated best with antibacterial activity compared to $fAUC/MIC$ and fC_{max}/MIC . The urine PK/PD target associated with a 1-log₁₀ bacterial reduction in urine is similar to that reported below by (Vingsbo Lundberg, 2022). As Vingsbo Lundberg et al. 2009 was an abstract no further assessment was made for the purposes of this review.
- A separate murine UTI study (using the same methodology described above) sought to characterize MEC PK/PD targets against 3 *E. coli* strains (MIC range: 0.5-96 mg/L) was conducted by the Applicant (Vingsbo Lundberg, 2022). The study evaluated MEC doses starting Day 3 after inoculation q8h or q12h with four different MEC doses (50 mg/kg, 6.25 mg/kg, and 2.5 mg/kg or 0.78 mg/kg). Urine, bladder, and kidneys were collected for CFU/mL determination on Day 5 after inoculation. MEC PK in mice was investigated using 18 female *E. coli* infected mice (MIC: 0.5 mg/L) dosed with MEC on Day 3 with 2.5 mg/kg SC. (Vingsbo Lundberg et al. 2009). Mean urine PK/PD targets of 20% associated with a 1-log₁₀ bacterial reduction in urine and 50% for a 2-log₁₀ bacterial reduction in urine were found when pooling strains (n=3; Vingsbo Lundberg, 2022). In this animal model, a CFU decrease was observed without treatment. The Applicant argues that a 1-log kill is appropriate to consider similar efficacy as with stasis in the systemic thigh infection model, however no data is provided to support this.
- Antibacterial effects of humanized MEC exposures were evaluated against 6 *E. coli* isolates with MICs between 0.5 mg/L and 64 mg/L (Zykov et al. 2020). Humanized dosing was

aimed at matching the MEC area under the concentration-time curve (AUC) in mice urine that is comparable to human volunteers receiving two human dosing regimens of PIV (200 mg and 400 mg three times daily [TID]). Activity to treat UTIs in mice was evaluated against clinical *E. coli* strains, including isolates producing ESBLs (CTX-M-14 and CTX-M-15), plasmid mediated AmpCs (CMY-4 and CMY-6), and carbapenemases (NDM-1 and VIM-29). Both dosing regimens reduced the number of CFU/mL in urine for all strains, including MEC resistant strains. No significant differences in effect between dose levels was observed, but a highly significant difference was observed between treated mice compared to the vehicle-treated mice for all three fluids/organs (urine, bladder tissue, kidney tissue). Similar MEC findings at a 400 mg twice daily (BID) humanized dose against 2 ESBL-producing *E. coli* (CTX-M9 and CTX-M15) was also shown ([Frimodt-Møller N et al. 2008](#)). As Frimodt-Møller et al. 2008 was an abstract no further assessment was made for the purposes of this review.

14.2.2. Human Relative Bioavailability of Oral Pivmecillinam Formulations

Bridge Between To-Be-Marketed and Clinical Trial/Study Formulations

For all the key/pivotal clinical studies, the formulation evaluated was either the 1981 to 1998 formulation or a formulation that is supported by a chemical/CMC bridge. (b) (4)

See the Biopharmaceutics review dated February 27, 2024, in Panorama for additional details. The PK parameter values listed in this review and in the Table 2 under Section 12.3 Pharmacokinetics of the review team proposed U.S. prescriber's information is from Heikkilä et al. 1992 (See Section 14.2.3) ([Heikkilä et al. 1992](#)). Heikkilä et al. 1992 used the same formulation (1981-1999 tablet) that was evaluated in Nicolle 2002 ([Nicolle et al. 2002](#)) (one of the supportive efficacy and safety studies) and that is bridged to the formulation evaluated in the three primary efficacy studies ([Menday 2000](#); [Ferry et al. 2007](#); [Vik et al. 2018](#)) and two of three safety studies ([Menday 2000](#); [Vik et al. 2018](#)).

Formulation Development History

The original formulation was developed as a capsule formulation (1975 capsules) that was replaced by a tablet formulation in 1977 (1977 Tablet), which subsequently underwent further optimization into a film-coated tablet in 1981 (1981 Tablet).

Since 1981, for subsequent formulation the (b) (4) and only minor (u) (4) have been introduced until this date. These three reformulated subsequent film-coated tablets are: 1981 to 1999 tablet, 2000 tablet, and 2007 tablet formulations. The chemical reformulations/ optimizations are considered by the Biopharmaceutics review team to not to have any impact on the PK. (b) (4)

See the Biopharmaceutics review dated February 27, 2024, in Panorama for more details.

Several clinical studies were conducted to evaluate and compare the bioavailability of different PIV formulations. The comparative bioavailability findings are summarized below as these findings provided additional supportive information for the purposes of this review.

Study (Leo 1977)

Study Design

The study objective was to compare the MEC bioavailability (BA) of a single 400 mg PIV dose administered as two 200 mg PIV film-coated tablets and as two 200 mg PIV gelatin capsules. BA was assessed based on serum concentrations and urinary excretion of MEC. The study was conducted at a single clinical center in 10 healthy adult volunteers receiving single-dose crossover administrations of both tablet (n=9) and capsule (n=10) formulations on two separate occasions on an overnight fast and not allowed to take food until after the two-hour PK blood sample.

Drug Product Formulations

Clinical report is signed in 1977 and therefore, the Applicant presumes that the study medication has the same composition and manufacturing facility as the commercial product at that time, i.e., the formulations are presumed to be the 1975 capsule and the 1977 tablet formulations as it states “film-coated tablets” and “gelatin capsules” in materials and methods section, respectively.

PK Sampling

Blood samples were obtained prior to administration of study drug, and 0.25, 0.5, 1, 2, 3, 4, and 6 hours after dosing. Urine was collected over the course of the following post dose intervals: 0 to 6 and 6 to 24 hours.

Bioanalytical Method

Serum and urine samples were analyzed for MEC using the bioassay method with *E. coli* Leo HA2 as the test organism and a standard preparation of MEC HCL dihydrate as the reference compound. No bioanalytical validation or study report submitted. Therefore, the review team could not assess whether the bioanalytical method is well characterized, appropriately validated, or documented to ensure reliable data to support regulatory decisions. Therefore, for the purposes of this review, only qualitative summary findings are discussed below.

Results

The study data indicated that similar MEC disposition can be expected after administration of PIV 1977 film-coated tablets compared to PIV gelatin 1975 capsules. The time to maximum concentration (T_{max}) was approximately 1 hour and cumulative excretion during first 6 hours (after dosing) was same as the cumulative excretion at 24 hours, regardless of the formulation.

Pivmecillinam HCL Tablets: Absorption Studies with Different Formulations

Study 1 ([Hey et al. 1982](#))

Study Design

The study objective was to compare the MEC BA of two different formulations of 200 mg PIV tablets by assessing serum concentrations of MEC in healthy volunteers receiving treatment following a fast or with light meal.

The study was conducted at a single clinical center in which eight (one female, seven males) healthy adult volunteers received single-dose crossover administrations of both tablet formulations on three separate occasions. The mean age was 33 (range 23 to 47) years. The mean weight was 72 (range 60 to 80) kg.

The treatment groups were:

- Two 200 mg PIV tablets (Ref), administered orally (PO) with 100 mL water after light meal (two pieces white bread with butter and marmalade plus a cup of coffee)
- One 400 mg PIV tablet (Test), administered PO with 100 mL water after light meal (two pieces white bread with butter and marmalade plus a cup of coffee).
- Two 200 mg PIV tablets (Ref), administered PO with 200 mL water, fast 16 to 18 hours
- One 400 mg PIV (Test), administered PO with 200 mL water, fast 16 to 18 hours

Drug Product Formulations

The article was received by journal in April 1981 and published in 1982. Therefore, the Applicant presumes that two formulations evaluated in this study are the 1977 tablet (Ref) and the 1981 tablet (Test) formulations as it states “conventional pivmecillinam chloride tablet, containing the excipient lactose” and “new oval pivmecillinam tablets containing microcrystalline cellulose” in materials and methods section, respectively.

PK Sampling

Blood samples were obtained prior to administration of study drug, and 0.25, 0.5, 0.75, 1, and 2 hours after dosing.

Bioanalytical Method Summary

Serum samples were analyzed for MEC using the bioassay method with *E. coli* Leo HA2 as the test organism and a standard preparation of MEC HCL dihydrate as the reference compound. No bioanalytical validation or study report submitted. Therefore, the review team could not assess whether the bioanalytical method is well characterized, appropriately validated, or documented in order to ensure reliable data to support regulatory decisions. Therefore, for the purposes of this review, only qualitative summary findings are discussed below.

Results

The study data indicated that the 1981 tablet formulation (i.e., the Test formulation with microcrystalline cellulose) yielded a higher C_{max} under fasting and fed conditions compared to

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the 1977 formulation (i.e., the Reference tablet with lactose). For both the formulations, a higher $C_{\max}$ was observed under fed condition. Note: due to the short sampling interval of two hours, the AUC is not considered for evaluations.

Study 2 (Roholt 1980)

Study Design

The study objective was to compare the MEC BA of two different formulations of 200 mg PIV tablets by assessing serum concentrations and urinary excretion of MEC. The study was conducted at a single clinical center in which 10 (7 females, 3 males) healthy adult volunteers received single-dose crossover administrations of both tablet formulations on two separate occasions following an overnight fast, subjects were not allowed to take food until after the 2-hour PK blood sample. The mean age was 45 (range 30 to 55) years. The mean weight was 67 (range 52 to 98) kg.

The two treatment groups were: two 200 mg PIV tablets containing lactose (ref.) and two 200 mg PIV tablets containing microcrystalline cellulose (test).

Drug Product Formulations

The study report is dated in 1980 and therefore, the Applicant presumes the 1977 tablet or the 1981 tablet formulation was used in this study.

PK Sampling

Blood samples were obtained prior to administration of study drug, and 0.25, 0.5, 1, 2, 4, 6, and 8 hours after dosing. Urine was collected over the course of the following post dose intervals: 0 to 6 and 6 to 24 hours.

Bioanalytical Method Summary

Plasma and urine samples were analyzed for MEC using the bioassay method with *E. coli* Leo HA2 as the test organism and a standard preparation of MEC HCL dihydrate as the reference compound. No bioanalytical validation or study report submitted. Therefore, the review team could not assess whether the bioanalytical method is well characterized, appropriately validated, or documented to ensure reliable data to support regulatory decisions. Therefore, for the purposes of this review, only qualitative summary findings are discussed below.

Results

The study data indicated that comparable MEC disposition can be expected after administration of either formulation of PIV tablets. It is noteworthy that unlike Hey 1982, these study findings did not suggest a difference in MEC bioavailability between the 1977 and 1981 formulations. $T_{\max}$ was approximately 1 hour for both the formulations and cumulative excretion during first six hours (after dosing) was same as the cumulative excretion at 24 hours, regardless of the formulation. These findings are in line with the findings from Leo 1977. However, it is notable that both studies were conducted by Leo Pharma, suggesting interlaboratory differences may have played a role. See also Section [14.3](#) Bioanalytical Method Validation and Performance.

14.2.3. Bioavailability and Pregnancy Effect on Pharmacokinetics

Study ([Heikkila et al. 1992](#))

Study Design

The study objective was to assess the PK of single-dose, intravenous (IV) administered 200 mg MEC or PO administered 200 mg PIV (Selexidin® tablet) to pregnant (n=27) and nonpregnant women (n=12).

Enrolled women were divided into five cohorts:

- Group A (n=11) early pregnancy (9-14 weeks gestation, 27 years mean age, 61 kg mean weight) hospitalized for pregnancy termination: Single-dose 200 mg MEC IV injection
- Group B (n=10) term pregnancy hospitalized for Caesarean section (39 to 40 weeks gestation, 32 years, 73 kg): Single-dose 200 mg MEC IV injection
- Group C (n=6) nonpregnant females of child-bearing age (26 years, 61 kg): Single-dose 200 mg MEC IV injection
- Group D (n=6) pregnant females (10 to 32 weeks gestation, 26 years, 62 kg) hospitalized for pregnancy termination (except for 1 subject): Single-dose 200 mg PIV PO after an overnight fast
- Group E (n=6) nonpregnant females of child-bearing age (32 years, 61 kg): Single-dose 200 mg PIV PO after an overnight fast

No subjects were administered antibacterials for at least 1 week prior to the study and none routinely used concomitant medications.

Subjects in Groups A and B received study medication 30 minutes prior to their surgical procedure. Subjects in Groups C, D, and E received study medication after an overnight fast.

Drug Product Formulations

The Applicant presumes that the PO formulation is the 1981 to 1998 formulation as the literature notes “pivmecillinam chloride (Selexidin, Lederle, Copenhagen, Denmark)” in the methods section. For all the key/pivotal clinical studies noted in this NDA, the formulation evaluated was either the 1981 to 1998 formulation or a formulation that is supported by a chemical/CMC bridge with the 1981 to 1998 formulation.

Blood Sampling

For subjects enrolled in Groups A, B, and C, blood samples for MEC PK evaluation were collected before and at 2, 5, 10, 15, 30, and 45 minutes, as well as 1, 2, 3, 5, and 8 hours after dosing.

For subjects enrolled in Groups D and E blood samples for MEC PK evaluation were collected before and at 15 and 30 minutes as well as 1, 2, 3, 5, and 8 hours after dosing.

Urine was collected from all subjects prior to dosing, and over the following intervals: 0 to 2, 2 to 5, and 5 to 8 hours after dosing.

Bioanalytical Method

Serum and urine samples were assayed for MEC concentrations by high-performance liquid chromatography (HPLC) using the method of Lee and Brooks, 1982 (See Section 14.3 Bioanalytical Method Validation and Performance). The limit of quantitation of MEC in plasma was 50 ng/mL, and in urine it was 1 µg/mL. The interassay coefficients of variations were 1.7% for plasma, and 1.5% for urine.

Results

Derived MEC PK parameters are presented in Table 62.

Table 62. Mean (SD) Mecillinam PK Parameters After a Single IV Dose of 200 mg Mecillinam and After a Single PO Dose of 200 mg Pivmecillinam HCL to Pregnant and Nonpregnant Women

PK Parameters	200 mg Mecillinam IV			185 mg Pivmecillinam PO	
	Early Pregnancy n=11	Term Pregnancy n=10	Nonpregnant n=6	Term Pregnancy n=10	Nonpregnant n=6
Total clearance (mL/min)	260±70	260±60	240±70	620±30 ^a	580±100 ^a
Renal clearance (mL/min)	167±57	192±14	186±41	210±85	230±60
V _d (L)	49±20 ^a	65±29 ^b	29±12 ^{a,b}		
AUC ₀₋₈ (µg min/mL)	816±191	786±126	918±292	253±108	214±44
C _{max} (mg/L)	19±9 ^a	29±14	34±18 ^a	1.8±1.1	1.7±1.1
T _{max} (min)	3±1.5	2.3±1	2±0	100±31	90±33
Elimination t _{1/2} (min)	133±38 ^a	107±41 ^b	75±21 ^{a,b}	57±34	61±32
Cumulative (0-8hr) % fe,u	66	72	81	28	39

Source: (Heikkilä et al. 1992), Table 2 and corresponding text, pg. 4.

^a and ^b indicate statistical significance (p<0.05) between the respective groups

Abbreviations: % fe, u, fraction (expressed as a percent) of the administered dose excreted in the urine; AUC, area under the concentration-time curve from time 0 to specified time after drug administration; CI, confidence interval; C_{max}, maximum plasma concentration of drug; IV, intravenous; mean, arithmetic mean; n, number of subjects within group; PK, pharmacokinetic; PO, oral; SD, standard deviation; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration; V_d, volume of distribution

Considering MECs fast absorption following PO administration (T_{max} approximately an hour and a half) and elimination (half-life approximately 1 hour), no significant MEC accumulation following PIV administration is expected in pregnant women and is in line with publicly available published repeat dose findings of MEC PK following PIV administration (data not reviewed here).

AUC and C_{max} were similar between pregnant women and nonpregnant women following PO administration of 200 mg PIV tablet. Approximate MEC bioavailability (F_{abs}, expressed as a percentage based on AUC estimates in Table 62) following oral PIV administration is 25% and 35% in nonpregnant and pregnant women, respectively. Note, the bioavailability estimate is based on comparison of dose normalized MEC exposure after 185 mg oral pivmecillinam administration and 200 mg IV MEC. Therefore, these calculations are not based on MEC equivalent doses.

The urine excretion data suggest that urinary excretion is the principal elimination pathway with approximately 10% lower urinary excretion during pregnancy following IV administration. Also, similar to the urinary excretion data summarized above in other studies, data from this study also

suggested that majority of drug was excreted in first five hours with 90 to 99% of total cumulative excretion ranging in first five hours, regardless of route of administration.

Overall, pregnancy effects on MEC PK following PIV PO administration are not clinically significant. No dose adjustment is recommended in pregnant woman.

Assessment of Additional Literature Data and Review Decision

PK findings from this study ([Heikkila et al. 1992](#)) are generally in line with two publicly available PK studies (Jeppesen et al. 1984 and [Roholt 1977](#)) and a study report (Leo Pharma, 1977) submitted by the Applicant. Therefore, the review team agrees with informing product labeling based on PK data from Heikkila et al. 1992 only as bioanalytical performance characteristics of the bioassay used to quantify MEC concentrations were not available/provided in the other studies listed here.

14.2.4. Single Ascending Dose Studies and Dose Proportionality

Study ([Roholt 1977](#))

Study Design

The authors have described four different clinical studies conducted in the same 9 to 11 subjects (7 females and 4 males). One of the studies characterized the dose proportionality of PIV in 10 healthy subjects. The age of subjects ranged from 33 to 55 years, and their weight ranged from 60 to 90 kg.

Subjects were administered each of the following treatments (focusing only on dose proportionality study):

- 200 mg PIV capsule (1x 200 mg)
- 400 mg PIV capsules (2x 200 mg)
- 800 mg PIV capsules (4x 200 mg)

Drug Product Formulation

The publication is from 1977 which is around the initial marketing of the product. No specific description of the formulation was provided for this study. The Applicant presumes that the drug formulation is the 1975 capsule formulation and is supported by the report's Table 4 heading ([Roholt 1977](#)).

PK Sampling

Suggested blood sampling schedule is such that blood samples were obtained 0.25, 0.5, 1, 2, 4, and 6 hours after dosing. Urine samples were collected during the intervals 0 to 6, and 6 to 24 hours after dosing.

Bioanalytical Method Summary

Plasma samples were assayed for MEC concentrations using bioassay with *E. coli* Leo HA2 as test organism. No bioanalytical performance characteristics were included. Therefore, for the purposes of this review, only qualitative summary findings are discussed below.

Results

Administration of oral PIV shows that $C_{\max}$ values increased by approximately 50% on doubling the dose, and AUC values approximately doubled directly proportionally with the dose. The $T_{\max}$ was delayed following 800 mg which suggested that a potential threshold value for the absorption mechanism may have been exceeded. The higher the dose, the lower the total cumulative urinary excretion over 24 hours suggesting exposure is less than dose proportional. In line with the other studies, cumulative excretion during first six hours (after dosing) was same as the cumulative excretion at 24 hours, regardless of the dose administered. Nevertheless, the review team concludes that data is inconclusive regarding dose proportionality given the limitations noted above related to bioanalytical method validation.

14.2.5. Human Food Effects on Pharmacokinetics

Three studies were conducted to evaluate the effect of food on PIV disposition. We focus here on two of these studies as [Parsons et al. 1977](#) utilized the capsule formulation and results were consistent with the other two studies.

Study 1 (Bornemann 1985, N2756A)

Study Design

The study (Bornemann 1985, N2756A) was conducted to determine the relative bioavailability of PIV in a fasting state, one hour prior to breakfast, with breakfast, and one hour after breakfast by assessing and comparing serum concentrations of MEC. The study was conducted at a single clinical center in which 18 healthy adult volunteers (12 males and 6 females) received single-dose crossover administrations of all four treatments (summarized below). For the enrolled subjects, the mean age was 26 (range 19 to 55) years, and the mean weight was 70.9 (range 48.6 to 84.5) kg. A drug-free washout period of one week separated each treatment. The standard breakfast consisted of six ounces of orange juice, two large eggs, one slice of toast with margarine and eight ounces of skimmed milk. The meal evaluated in this study is roughly aligned with the low-fat meal described in the FDA guidance for industry *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations* ([June 2022](#)).

The four treatment groups were:

- Treatment A: 400 mg PIV (two 200 tablets), fasting
- Treatment B: 400 mg PIV (two 200 tablets), one hour before breakfast
- Treatment C: 400 mg PIV (two 200 tablets), halfway through breakfast
- Treatment D: 400 mg PIV (two 200 tablets), 1 hour after breakfast

Drug Product Formulations

The study report is dated December 1984 and therefore, it is presumed that the formulation is the 1981 formulation as it is stated as 200 mg Coactabs tablets in the methods section.

PK Sampling

Blood samples were obtained prior to administration of study drug, and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8 and 10 hours after dosing. Urine was collected over the course of the following post dose intervals: predose, 0-2, 2-4, 4-6, 6-8, and 8-12 hours.

Bioanalytical Methods

Plasma and urine samples were analyzed for MEC using HPLC with UV Detection (See Section 14.3 Bioanalytical Method Validation and Performance).

Results

Derived MEC PK parameters are presented in Table 63 and the comparison of MEC exposures (C_{max} and AUC estimates) across the treatment groups in Table 64.

Table 63. Mecillinam Pharmacokinetic Parameters: 400 mg Pivmecillinam Tablets (2x200mg) in a Fasting State, Before, During, and After Breakfast (N=18)

PK Parameter Mean (SD)	Pivmecillinam Fasted (Treatment A)	Pivmecillinam Before Breakfast (Treatment B)	Pivmecillinam During Breakfast (Treatment C)	Pivmecillinam After Breakfast (Treatment D)
C_{max} (µcg/mL)	3.62 (0.9)	3.19 (0.6)	4.27 (0.5)	4.13 (0.9)
T_{max} (h)	1.2 (0.4)	1.4 (0.6)	1.3 (0.5)	1.7 (0.5)
AUC _{0-10h} (µg·hr/mL)	8.1 (2)	7.7 (1.8)	10 (1.8)	9.7 (1.8)
$t_{1/2}$ (h) ^a (CI)	0.98 (0.73-1.62)	1.04 (0.70-2.06)	0.94 (0.75-1.34)	0.88 (0.61-1.07)
Cumulative (0-24h) % fe,u	27 (8.5)	27 (12)	33 (6.8)	34 (12)

Source: Bornemann 1985, N2756A study report, Table 12, pg. 41/234.

^a Harmonic mean and range

Abbreviations: % fe, u, fraction (expressed as a percent) of the administered dose excreted in the urine; AUC, area under the concentration-time curve from time 0 to specified time after drug administration; CI, confidence interval; C_{max} , maximum plasma concentration of drug; h, hour(s); N, number of subjects in treatment arm; mean, arithmetic mean; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life; T_{max} , time to maximum plasma concentration

Table 64. Effect of Food and Timing of Meal on Mecillinam PK Following Oral Pivmecillinam Administration (N=18)

PK Parameter	GeoMean Ratio ^a With 90% CI		
	Treatment B/Treatment A	Treatment C/Treatment A	Treatment D/Treatment A
C_{max}	0.89 (0.80, 0.99)	1.20 (1.03, 1.40)	1.14 (0.96, 1.36)
AUC _{0-10h}	0.95 (0.85, 1.07)	1.24 (1.12, 1.38)	1.21 (1.08, 1.37)

Source: Bornemann 1985, N2756A study report, Tables 8-11, pg. 37-40/230-233

^a FDA reviewer performed analysis from individual data.

Abbreviations: AUC, area under the concentration-time curve from time 0 to specified time after drug administration; CI, confidence interval; C_{max} , maximum plasma concentration of drug; GeoMean, geometric mean; number of subjects in treatment arm; PK, pharmacokinetic

Findings reported in Table 64 suggest that food slightly increased bioavailability of MEC (25-35%), but not to clinically relevant extent. These findings are in line with the summary findings noted above from Hey 1982.

Study 2 (Leo Pharma 1977)

Study Design

This study (Leo Pharma 1977) was conducted to evaluate the effect of food on MEC PK when PIV is administered in healthy subjects in a fed versus fasted state. The nine healthy subjects were administered 200 mg PIV tablets on one occasion after an overnight fast. On another day, the same subjects were administered 200 mg PIV tablets in a fed state. The meal consisted of bread and butter, egg, milk, cheese, and coffee. The information on exact content of meal is not included in the study report.

The two treatment groups were:

- PIV tablets (200 mg), fasted
- PIV tablets (200 mg), fed

Drug Product Formulation

The study report was signed in 1977. Therefore, the Applicant presumes that the study medication has the same composition and used same manufacturing facility as the commercial product at that time, i.e., the 1977 tablet formulation, as “tablets of 200 mg of pivmecillinam hydrochloride” is stated in materials and methods section.

PK Sampling

Blood samples were obtained 0.25, 0.5, 1, 2, 3, 4, and 6 hours after dosing. Urine was collected over 0 to 2, 2 to 4, 4 to 6, and 6 to 24 hours postdose intervals.

Bioanalytical Method Summary

Serum was assayed using the bioassay method with *E. coli* Leo HA2 as the test organism and a standard preparation of MEC HCL dihydrate as the reference compound. No bioanalytical validation or study report submitted. Therefore, the review team could not assess whether the bioanalytical method is well characterized, appropriately validated, or documented in order to ensure reliable data to support regulatory decisions. Therefore, for the purposes of this review, only qualitative summary findings are discussed below.

Results

In the alignment with the food effect data summarized from other study above, food slightly increased MEC bioavailability, but not to a clinically relevant extent.

14.2.6. Human Drug-Drug Interactions

The impact of concomitant administration of probenecid (OAT3 inhibitor) and PIV has been studied in two clinical studies ([Roholt et al. 1975](#); [Andrews et al. 1976](#)).

Study 1 ([Andrews et al. 1976](#))

Study Design

This study was conducted to assess the effect of different factors on MEC PK after single or multiple doses of PIV capsules. The study was divided into five parts to investigate different factors (bed rest, six-day course, and probenecid). This review focuses on the effects of concomitant administration of probenecid (1000 mg) on MEC PK after a single dose of 400 mg PIV given as two 200 mg capsules.

The study included 6 healthy subjects aged between 20 and 25 years. Two 500 mg tablets of probenecid were given by mouth 30 minutes before the PIV capsules. Their bladder was emptied, and a blood sample (5 mL) taken immediately before the drug was administered.

Drug Product Formulation

The article was received by journal 1975 and published in 1976. As the article is from or before 1975, and the method section states, “capsules containing pivmecillinam”, a capsule formulation is used. It is not clear if it is the 1975 gelatin capsule formulation.

PK Sampling

Blood was collected at 15, 30, 45, and 60 minutes and then at 1.5, 2, 2.5, 3, 4, and 6 hours. In each case, a 2 mL sample was discarded before collecting the sample for analysis. A urine sample was collected for analysis at 6 hours.

Bioanalytical Method Summary

Serum and urine samples were assayed in triplicate for MEC by a bioassay using the *E. coli* Leo HA2 as test organism. The method has an accuracy of better than $\pm 20\%$ at the 95% confidence limit. MEC HCL dihydrate was used as a reference standard but the results are expressed as $\mu\text{g/mL}$ of anhydrous MEC/mL serum or as percentage of administered dose. No further bioanalytical performance characteristics of the bioassay are specified. Therefore, for the purposes of this review, only qualitative summary findings are discussed below.

Results

Probenecid inhibited drug elimination via renal excretion /urinary elimination. The systemic increase in MEC exposures was observed with approximately 40% relative increase in C_{max} and 83% increase in AUC. See Section [8.2.2](#) for the review team’s recommendations for labeling.

Study 2 ([Roholt 1977](#))

Study Design

As noted above, within Roholt, 1977, the authors have described four different clinical studies. One of the studies characterized the contribution of tubular excretion on MEC disposition, as summarized in this section. This study evaluated a single dose of oral 400 mg PIV with and without 1000 mg probenecid in 11 healthy, fasting adult subjects with weight ranging from 60 to 80 kg.

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The treatment groups were:

- 400 mg PIV PO
- 400 mg PIV+1000 mg probenecid PO

Drug Formulation

The publication is from 1977, which is around the initial marketing of the product. No specific description of the formulation was provided for this study. The Applicant assumes the drug formulation is either the 1975 capsule formulation or 1977 tablet formulation.

PK Sampling

Blood samples were collected over a period of 6 to 8 hours after dosing and urine was collected over 0 to 6, and 6 to 24 hours postdose intervals. All samples were assayed for MEC.

Bioanalytical Method Summary

Serum and urine were assayed using the bioassay method with *E. coli* Leo HA2 as the test organism and a standard preparation of MEC HCL dihydrate as the reference compound. No bioanalytical performance characteristics were included. Therefore, for the purposes of this review, only qualitative summary findings are discussed below.

Results

In the presence of probenecid, the renal clearance of MEC is reduced, suggesting that tubular secretion contributes to the elimination of MEC. While the numeric C_{max} values (associated with the same dose) between this and the aforementioned DDI study were different, the relative change and in C_{max} and AUC estimates were comparable. These findings further support the review team's conclusion that significant interlaboratory variability may have an effect on the reported numerical values either due to collection or bioassay methods. See also Section [14.3 Bioanalytical Method Validation and Performance](#) and Section [8.2.2](#) for the review team's recommendations for labeling.

14.2.7. Human Renal Impairment

For MEC, where renal clearance is the main elimination pathway, the most important factor that may affect its clearance is a subject's renal function. A total of nine clinical studies were submitted by the Applicant to assess the impact of renal impairment on MEC disposition including during hemodialysis (Patel et al. 1979; [Nakano H. et al. 1977](#); [Bailey et al. 1980](#); [Svarva and Wessel-Aas 1980](#); [Schapira 1984](#); [Patel et al. 1985](#); [el-Guinedy et al. 1986](#); [Moukhtar et al. 1987](#); Denneberg et al. 1975, partly published in [Ekberg et al. 1978](#)). The clinical pharmacology review team focused on four clinical studies (Patel et al. 1985 and Svarva et al. 1980 following intravenous MEC and Ekberg et al. 1978 and Nakano et al. 1977 following oral PIV). The other studies demonstrated similar PK and safety/tolerability findings and were therefore not reviewed in detail here due to various limitations (e.g., limitations related to study design, sample size, bioanalytical method).

Study 1 ([Patel et al. 1985](#))

Study Design

This study was conducted to assess the impact of renal impairment on the PK of MEC after a 15-minute IV infusion of MEC (10 mg/kg). The study enrolled 5 healthy subjects with normal renal function and 31 subjects with various degrees of renal impairment. Specifically, subjects were divided into the following groups: five healthy subjects (creatinine clearance [CrCl], above 100 mL/min), five subjects with mild renal impairment (CrCl, 51 to 100 mL/min), nine subjects with moderate renal impairment (CrCl, 16 to 50 mL/min), nine subjects (not maintained on dialysis procedures) with severe renal impairment (CrCl, 5 to 15 mL/min), and eight subjects on dialysis, five of whom were maintained on hemodialysis and three of whom were maintained on peritoneal dialysis. The age of the subjects ranged from 25 to 64 years, and their body weight ranged from 43 to 113 kg. The dialysis subjects received the drug on the day of the dialysis procedure. The hemodialysis subjects were dialyzed for 4 h immediately after the end of drug infusion.

PK Sampling

Blood samples were obtained prior to administration of study drug, and at 5, 10, 15, 20, 25, 30, and 45 minutes after the start of the infusion, then 1, 1.5, 2, 3, 4, 6, and 8 hours after the end of the infusion. Urine was collected over the course of the following postdose intervals: -2 to 0 (predose), 0 to 2, 2 to 4, 4 to 6, 6 to 8, and 8 to 24 hours after dosing.

Bioanalytical Method Summary

Plasma, urine, and dialysate specimens were analyzed for amdinocillin by a microbiological assay on a large plate with *E. coli* Leo HA2 as a test organism. The plasma and urine assay were linear from 0.5 to 8 µg/mL, with a limit of detection of 0.1 µg/mL. The interassay precision for plasma was 11.7% at the 10 µg/mL concentration and 14.1% at the 100 µg/mL concentration after appropriate dilution with water. The interassay precision for urine averaged 6.7% over the 10 to 2,000 µg/mL range.

Results

Derived plasma PK parameters from MEC plasma and urine concentrations are presented in [Table 65](#). It was not possible to calculate PK parameters of amdinocillin in hemodialysis subjects either during or after hemodialysis, because the hemodialysis treatment was initiated during the distribution phase, which generally lasts up to 2 hours (3, 4, 7), and blood sampling during the post hemodialysis period (6 to 10 hours) was limited.

Table 65. Mean±SD (Range) Plasma Mecillinam PK Parameters: Healthy Subjects and Renally Impaired Subjects After 10 mg/kg IV Administration

Group (n in Group) and CrCl Range	t _{1/2} (Hours)	AUC (µg·hr/mL)	V _d (mL/kg)	CL _{plasma} (mL/min)	CL _{renal} (mL/min)	% fe, u
Healthy (5) ≥100 mL/min	1.1 (0.9-1.3)	30.7±15 (15.6-55.6)	588±221 (297-871)	420±143 (201-600)	218±102 (122-335)	44±18 (28-65)
Mild renal impairment (5) 51-100 mL/min	1.3 (0.7-2.8)	65.9±29.2 (26.2-90.1)	394±188 (240-655)	289±152 (189-515)	126±62.6 (79.1-218)	42±6.1 (36-51)
Moderate renal impairment (9) 16-50 mL/min	2.4 (1.7-3.3)	116±34.8 (61.2-181)	333±112 (224-576)	118±46.1 (63.8-212)	28.4±16.5 (6.5-57.9)	23±12 (10-41)
Severe renal impairment (9) 5-15 mL/min	4 (2.7-6.4)	150±49.7 (81.6-243)	443±144 (262-689)	86.3±26.1 (66.7-153)	9±6.5 (4-23.6)	9.6±4 (5.1-16)
Dialysis						
Hemodialysis (5)	NC	NC	NC	NC	NC	53±20 (32-72)
Peritoneal (2)	4.5, 4	144, 145	447, 400	83.3, 74.7	NC	2.4, 3.7 ^a

Source: (Patel et al. 1985), Table 2, pg. 48

^a percentage recovered in dialysate

Abbreviations: % fe, u, fraction (expressed as a percent) of the administered dose excreted in the urine; AUC, area under the concentration-time curve from time 0 to specified time after drug administration; CL_{plasma}, plasma clearance; CL_{renal}, renal clearance; CrCl, creatinine clearance; mean, arithmetic mean; N, number of subjects in treatment arm; NC, not calculated; PK, pharmacokinetic; SD, standard deviation; t_{1/2}, half-life; V_d, volume of distribution

The maximum concentration in healthy adults was approximately 30 µg/mL and in moderate or severe renal impairment was 40-50 µg/mL. Systemic MEC concentrations increased (based on AUC) relative to renal impairment severity. The AUC ratios are 2.15 (mild/healthy), 3.77 (moderate/healthy), and 4.88 (Severe/healthy). One volunteer experienced moderate headache, moderate nausea, vomiting, and mild diarrhea, which was possibly drug-related. The headache was relieved with an analgesic; the other symptoms subsided the same day without medication. No clinically significant laboratory abnormalities were reported.

Study 2 (Svarva and Wessel-Aas 1980)

Study Design

This study was conducted to assess the impact of severe renal impairment on serum MEC concentrations during a repeat course of IV administered MEC (400 or 600 mg MEC administered every 6 hours; only 1 subject received 600 mg MEC). No dosing adjustment was made for renal function or body weight.

The study enrolled 12 (7 male and 5 female) renally impaired subjects (CrCl ranging from <0.5 to 16 mL/min) suffering from UTI requiring antimicrobial therapy. The age ranged from 23 to 82 years.

PK Sampling

Blood samples for MEC analysis were obtained on Day 2 and Day 5 of therapy 0.75, 1.5, 4, and 6 hours after dosing.

Bioanalytical Method Summary

Serum and urine samples were assayed for MEC concentrations using a bioassay with paper disc diffusion method with *E. coli* Leo HA 12 as a test organism. Standard discs were impregnated

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with aqueous solutions of MEC HCL dihydrate with standards ranging from 1 to 10 µg/mL. No bioanalytical performance characteristics were mentioned. Therefore, for the purposes of this review, only qualitative summary findings are discussed below.

Results

MEC accumulation ratio ($C_{\max, \text{Day 5}} / C_{\max, \text{Day 2}}$) based on mean concentration values is between 1.38 (0.75 hr postdose) to 1.27 (6 hr postdose). The authors note that there was no statistical difference between Day 2 and Day 5 values.

No side effects were observed in the subjects studied in spite of very high serum levels of the antibacterial. The Authors state “mecillinam can be given safely and in normal doses for short term treatment of subjects with renal insufficiency, even when the renal function is severely reduced.”

Study 3 ([Ekberg et al. 1978](#))

Study Design

This study was designed to assess the impact of renal impairment on the PK of MEC after orally administered 450 mg PIV (3x 150 mg) capsules administered with a meal or plain fluid. The study enrolled 20 subjects in total including, 12 male and 3 female renally impaired subjects (serum creatinine ranging from 1 to 14.7 mg/100 mL) and 5 dialysis male subjects (serum creatinine ranging from 11.9 to 19 mg/100 mL). The mean age of renally impaired subjects was 49 (26 to 65) years, and the mean age of the dialysis subjects was 45 (30 to 64) years.

PK Sampling

Blood samples for PK analysis were obtained prior to administration of study drug and 0.25, 0.5, 1, 2, 4, and 6 hours after dosing. Urine was collected over the interval of 0 to 6 hours after dosing in the renally impaired (not on dialysis) subjects.

Bioanalytical Methods Summary

Serum and urine samples were assayed for MEC concentrations using the bioassay method with MEC as a standard. Bioanalytical performance characteristics were not provided. Therefore, for the purposes of this review, only qualitative summary findings are discussed below.

Results

This study evaluated 450 mg PIV (2.25 times the proposed dose) dose. Given that body weight was not given, individualized creatinine clearance could not be calculated. However, it is noteworthy that from the enrolled 15 subjects, 3 individuals had serum creatinine value above 3 mg/dL. In these 3 individuals, urine recovery of first 6 hours was significantly reduced, compared to the rest of 12 subjects.

Study 4 ([Nakano H. et al. 1977](#))

Study Design

This study was designed to assess the impact of renal impairment on the PK of MEC after orally administered 146.2 mg PIV, 4 times daily (QID), for 7 days. The study enrolled 10 renally impaired subjects [CrCl ranging from 9.4 to 84.2 mL/min]. The mean age of renally impaired subjects was 59.7 years (Group 1), 54.2 years (Group 2), and 64.5 years (Group 3). The mean weight of renally impaired subjects was 54.1 kg (Group 1), 50.7 kg (Group 2), and 48.5 kg (Group 3).

PK Sampling

Blood samples for PK analysis were obtained prior to administration of study drug and 0.5, 1, 2, 4, and 6 hours after dosing. Urine was collected at intervals of 0 to 3, 3 to 6, 6 to 12, and 12 to 24 hours after dosing.

Drug Analysis

Serum and urine samples were assayed for MEC concentrations using the bioassay method with MEC as a standard. Bioanalytical performance characteristics were not provided. However, because of study relevance, results are discussed below but some uncertainty exists.

Results

PK findings are presented in [Table 66](#) and [Table 67](#).

Table 66. Summary of Mean (SD) Serum and Urine Mecillinam Concentrations (µg/mL) in Three Groups of Subjects With Renal Impairment After Oral Pivmecillinam Administration

		Renal Impairment		
		Group #1 CrCl: 73-84 mL/min n=3	Group #2 CrCl: 35-47 mL/min n=3	Group #3 CrCl: 9-15 mL/min n=2 ^a
Time After Dosing (h)	Dose			
Plasma PK				
0	Single	-	-	-
	Multiple	<0.1	0.16 (0.12)	1.11
0.5	Single	0.36 (0.06)	0.67 (1.19)	0.69
	Multiple	0.62 (0.44)	0.66 (0.77)	1.59
1	Single	0.5 (0.2)	0.8 (1.19)	1.11
	Multiple	0.78 (0.64)	0.91 (0.68)	1.95
2	Single	0.43 (0.27)	0.79 (0.57)	1.14
	Multiple	0.49 (0.57)	0.65 (0.38)	1.79
4	Single	0.13 (0.04)	0.28 (0.12)	0.83
	Multiple	0.19 (0.13)	0.22 (0.19)	1.21
6	Single	<0.1	<0.1 (0.04)	0.55
	Multiple	<0.1	0.12 (0.04)	0.94
Urine PK				
0-3	Single	75.7 (51.6)	29.6 (17.7)	12.1
	Multiple	56.3 (24.2)	89.9 (79.1)	23.3
3-6	Single	28.7 (12.1)	19.4 (19.3)	12.1
	Multiple	32.7 (43.7)	32.7 (43.7)	14.6
6-12	Single	3.3 (2.6)	4.7 (4.6)	5.6
	Multiple	1.4 (1.3)	8.8 (13.1)	15.6
12-24	Single	<0.1	1.1 (2.1)	1.6
	Multiple	0.7 (1)	4.5 (6.9)	4.1

Source: (Nakano H. et al. 1977), Tables 2 and 3, pg. 286.

^a Standard deviation not included as sample size was less than 3.

Abbreviations: CrCl, creatinine clearance; h, hour(s); n, number of subjects within group; PK, pharmacokinetic; SD, standard deviation

Table 67. Summary of Mean (SD) Mecillinam Serum and Urine Concentrations, PK Parameters, and Fold Changes in Three Groups With Various Degrees of Renal Impairment After Oral Pivmecillinam Administration

		Renal Impairment		
		Group #1 CrCl: 73-84 mL/min n=3	Group #2 CrCl: 35-47 mL/min n=3	Group #3 CrCl: 9-15 mL/min n=2
Time After Dosing (h)	Dose			
Plasma PK				
C _{max} (µg/mL)	Single ^a	0.53 (0.19)	1.05 (1.06)	1.14
	Multiple ^b	0.79 (0.62)	0.96 (0.68)	1.99
C _{max} AR	Multiple/Single	1.49	0.91	1.74
C _{max} FC	Multiple #2 or #3/#1 ^c	--	1.21	2.52
AUC (µg•hr/mL)	Single ^{a, c}	1.51	2.73	5.10
	Multiple ^{b, c}	2.07	2.60	8.58
AUC AR	Multiple/Single ^c	1.4	0.95	1.68
AUC FC	Multiple #2 or #3/#1 ^c	--	1.25	4.14
Urine PK				
C _{max} (µg/mL)	Single ^a	75.7 (51.6)	33.7 (18.1)	14.6
	Multiple ^b	56.3 (24.2)	93.1 (79.7)	23.6
AR	C _{max} , multiple/C _{max} , single	0.74	2.75	1.61

Source: (Nakano H. et al. 1977), Tables 2 and 3, pg. 286.

^a Plasma and urine were obtained after a single dose of 146. 2 mg PIV (equimolar to 100 mg Mecillinam).

^b Plasma and urine were obtained after final dosing on Day 7 of 146. 2 mg PIV four times per day for a week.

^c Reviewer's independent analysis of mean data. Individual subject level data not available.

Abbreviations: (--), not calculated; AR, accumulation ratio; AUC, area under the concentration-time curve from time 0 to 6 hr after drug administration; C_{max}, maximum plasma concentration of drug; CrCl, creatinine clearance; FC, fold change; mean, arithmetic mean; n, number of subjects within group PK, pharmacokinetic SD, standard deviation

Mean serum MEC concentrations increased as a result of the degree of renal impairment. Urine concentrations decreased as a result of the degree of renal impairment. The authors state that the majority of maximum observed concentrations occurred within three hours. MEC accumulation following multiple dosing (146 mg PIV QID for 7 days) was no greater than 1.74 times that following a single dose. An estimate of MECs half-life in subjects with CrCl <30 mL/min is roughly 2.4 hr based on the following relationships:

Figure 2. Steps to Obtain Half-Life ($t_{1/2}$) From Accumulation Ratio Estimate

$$\text{Accumulation ratio} = \frac{1}{1 - e^{-k \cdot \text{tau}}}$$

$$t_{1/2} = \frac{0.693}{k}$$

Abbreviations: e, mathematical constant; k, rate constant; $t_{1/2}$, half-life; tau, dosing interval

Assessment of Risk Based on the Literature Influence and Decision Consequence

The following is summary of available information on oral PIV and IV MEC use in subjects with renal impairment:

- Single IV MEC doses of up to 15 mg/kg and multiple IV MEC dosing of 400 mg every four hours have been studied in subjects with some degree of renal impairment (n=85). Thirty-nine of those individuals had creatinine clearance < 30 mL/min. Twelve of those individuals received every four hours repeat dosing for five days.
- Oral PIV of up to a single 450 mg PIV dose and multiple oral PIV dosing of 146.2 mg PIV (0.73 times the proposed dose) every 4 times daily for 7 days have been studied in subjects with some degree of renal impairment. With the single 450 mg oral PIV dose, there were 11 individuals with serum creatinine above 1.2 mg/dL and 8 individuals with serum creatinine above 3 mg/dL. Body weight was not given, so individualized creatinine clearance could not be provided. With multiple dosing, two individuals had creatinine clearance <30 mL/min.
- Intravenously administered single and repeat-dose MEC have been well tolerated in individuals with severe renal impairment. Orally administered single and repeat-dose PIV have been well tolerated in individuals with severe renal impairment. Accumulation ratio ($C_{\text{max, Day 7}} / C_{\text{max, Day 1}}$) was 1.74 with 4 times daily dosing for 7 days in subjects with creatinine clearance < 30 mL/min. The oral multiple dose findings suggest a 21% and 152% increase in mean MEC C_{max} as well as a 25% and 314% increase in mean MEC AUC in subjects with CrCl 35-47 mL/min and 9-15 mL/min, respectively. However, the observed highest effect in mean MEC AUC estimates in subjects with CrCl: 9-15 mL/min, is approximately 28% and approximately 6% of AUC estimates reported in healthy subjects and in subjects with severe renal impairment, respectively, following 10 mg/kg MEC IV administration ([Patel et al. 1985](#)). These estimates are reasonable to consider for the proposed dosing regimen of 200 mg PIV TID, as the difference in dose is modest (27%; 200 mg versus 146.2 mg) and there is a longer time period of drug elimination (TID versus QID). Furthermore, projected MEC concentrations with the proposed PIV dosage regimen of 200 mg PIV TID are not anticipated to be higher than intravenous MEC concentrations,

which were found to be well tolerated in both the general population and subjects with renal impairment.

Overall, there is no or low risk to anticipated clinical safety due to approximately two-fold higher systemic MEC concentrations following oral PIV in individuals with severe renal impairment with an unadjusted PIV dosing regimen of 200 mg TID. There is a hypothetical increased risk to anticipated clinical efficacy loss due to reduced MEC excretion in urine secondary to renal dysfunction. Taken together all the information provided by the Applicant, no dosage adjustment can be recommended.

14.3. Bioanalytical Method Validation and Performance

In clinical studies summarized above, MEC concentrations were measured by a bioassay or HPLC bioanalytical methods ([Lee and Brooks 1982](#)). Only the HPLC method was adequately validated, and supportive information was included related to dilution linearity, extraction efficiency (recovery), precision, accuracy. Sample storage, and sample processing were conducted within time frame windows supported by stability data. The bioanalytical method and validation results are summarized in [Table 68](#).

Note, the Applicant has submitted a comparison between the bioassay approach and HPLC method of Lee and Brooks, which consisted of data from two healthy subjects and citing reasonable correspondence between the two analytical methods by correlation analyses. While data are suggestive that the two methods align, a cross-validation can't be established due to two issues:

1. There is insufficient data submitted to validate the bioassay bioanalytical method.
2. A more robust cross validation evaluation is required with study sample concentrations ($n \geq 30$) measured using both methods, different matrices (plasma and serum), and from each of the bioanalytical laboratories used in submitted PK reports ([November 2022](#)).

From the individual study assessments above, the reviewer notes that PK parameters estimates (e.g., C_{max} and AUC) varied by investigator/laboratory.

Table 68. Summary of Mecillinam Bioanalytical Method Validation and Performance

Drug	Mecillinam	
Biological matrix	Plasma	Urine
Extraction methods	Protein precipitation extraction	
Internal standard	Azidocillin	
Validation range	0.5 to 100 µcg/mL	0.025 to 5 mg/mL
Interday accuracy (RE%) ^a	-6 to 3.5a	-4 to 1a
Interday precision (CV%) ^a	≤3.5a	≤1.7a
Validation report	(Lee and Brooks 1982)	
Study	(Heikkila et al. 1992)	
Internal standard	Azidocillin	
Limit of quantitation	0.05 µg/mL	1 µg/mL
Interday precision (CV%) ^a	≤1.7	≤1.5
Study	Bornemann 1985, N2756A	

Drug	Mecillinam	
Biological matrix	Plasma	Urine
Internal standard	Azidocillin	
Limit of quantitation	0.5 µcg/mL	250 µcg/mL
Interday precision (CV%) ^a	≤8.3	≤3.38

Source: Bornemann 1985

^a Interday accuracy (RE%) and Interday precision (CV%) were calculated manually by the reviewer from Table 2 and 3, pg. 143-144. Abbreviations: CV%, coefficient of variation expressed as a percentage; RE%, relative error expressed as a percentage

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not Applicable

14.5. Pharmacometrics Assessment

14.5.1. Review Summary

Pivmecillinam (PIV), a prodrug of MEC, is a beta-lactam antibacterial active against select gram-negative pathogens. The Applicant is seeking an indication for treatment of uUTI. This submission consists of several population pharmacokinetic (PopPK) analysis reports, including those with preliminary subsets of data (analysis by (b) (4)); however, the pharmacometric review focus is placed on the final report on PopPK model and probability of target attainment (PTA) (analysis by (b) (4)). In this pharmacometric assessment, “pivmecillinam” refers to the oral drug product (unless otherwise specified for intravenous or IV route).

PK studies of oral PIV and IV MEC primarily consisted of phase 1 studies in healthy volunteers. The PK studies evaluated oral PIV and IV MEC exposures as functions of administration routes, formulation, food effect, and renal function (derived via the Cockcroft-Gault formula). Because most of the clinical pharmacology studies were conducted in the 1980s, several considerations pertinent to sample handling, bioanalytical methods, PK data reliability, and clinical context should be acknowledged for the PK analysis. To support the proposed indication of PIV, a PopPK analysis was conducted to characterize drug exposure in plasma, serum, and urine. The final PopPK model was used to conduct simulations for clinical scenarios and to perform PTA analysis. The following limitations related to the PK data (used in the development PopPK model) were identified:

1. Unvalidated bioanalytical assays,
2. Large proportions of missing covariates, and
3. Clinical relevance of imputed covariates in the context of female uUTI.

Overall, these limitations impact the quality of the imputed PK dataset and hinders the utility of the final PopPK model in describing the PK characteristics and supporting dose recommendation. The various issues identified in the final imputed PK dataset (summarized in the following section) and the aforementioned limitations collectively preclude an accurate assessment, interpretation, and generalizability of drug exposure, covariate impacts, and urinary PTA analysis in the setting of clinical relevance and the target subject population.

14.5.2. Introduction

The objectives of the PopPK analysis were to:

- Develop a PopPK model to describe the disposition and urine excretion of PIV and MEC
- Evaluate the covariate impacts
- Predict PTA in different clinical scenarios

14.5.3. Model Development

Data

The PopPK analysis was based on data from 15 studies. An overview of study type, drug dosage, and population is briefly summarized in [Table 69](#). The final NONMEM dataset includes 3,964 evaluable plasma PK observations from 228 subjects (after excluding 1,376 BLQ observations, 90 observations missing at random, and 1 outlier observation) and 989 urine PK observations from 177 subjects. A summary of subject demographics by disease state is provided in [Table 70](#). Of note, Study 8 in the final submitted dataset was a substudy of Study 7 that was also included, and therefore, PK data from Study 8 were omitted for the PopPK model developed.

Bioanalytical Assay and Matrix Effect

The lower limits of quantification in plasma or serum varied across studies and specific values were not available for nine studies. Additionally, some plasma concentrations were reported as “extrapolated from standard curve.” Therefore, the lower limits of quantification were assumed by the Applicant based on available PK data. With respect to matrix effect, as described in [Table 71](#), PK samples were assayed in both serum and plasma matrices; however, the matrix effect was not evaluated. Lastly, inadequate information was provided to support bioanalytical assays using the bioassay methods utilized for PK quantification (See Section [5.2](#) Clinical Pharmacology/Pharmacokinetics and [14.3](#) Bioanalytical Method Validation and Performance for additional details).

Missing Covariates and Covariate Prediction

A large proportion of the subjects had missing covariate values and were imputed based on distributions of the available covariates. [Table 72](#) briefly summarizes the missing covariates by studies. Out of 228 subjects in the final PK dataset, body weight information was available for 116, age for 152, and sex for 180 subjects. Subsequently, derived CrCl was available for 52 subjects. Based on prior knowledge for other beta-lactam antibacterials, body weight and CrCl were expected to influence PIV PK.

As such, the Applicant developed a covariate prediction model to describe the correlation between available covariates. This covariate model was used to predict individual missing covariate values using the distributions and correlations observed in the other studies. These covariates were appended to the analysis dataset for use in the subsequent PK analysis. Densities of age, body weight, and serum creatinine (SCR) for the actual values and final actual plus predicted values are illustrated in [Figure 3](#). Sex was modeled as a proportion of male subjects

(based on study protocol of percentage of male subjects enrolled but with missing subject level information), and the frequencies of each predicted assignment are shown in [Figure 4](#).

The FDA pharmacometrics review team's assessment of the PK dataset was limited by variations in bioanalytical assay, matrix effect, missing covariates, and covariate prediction.

The variations in bioanalytical assay and the limitations/uncertainties noted in Section [14.2](#) under "In Vivo Studies related to assay performance across clinical PK studies" may impact the accuracy of quantification of PK observation and the quality of final PK dataset. Also, plasma concentrations being reported as "extrapolated from standard curve" should be clearly identified and removed prior to PK analysis. The lack of evaluation of matrix effect is further discussed in Section [14.3](#) Bioanalytical Method Validation and Performance.

Regarding covariate missingness, several factors should be considered. PIV is primarily excreted renally, and CrCl is known to influence drug disposition; however, CrCl (as derived by Cockcroft-Gault formula in this submission) is also dependent on individual age, body weight, SCR, and sex. Any missing component could impact the derivation and accuracy of CrCl in the setting of large proportions of missing covariates. In the final dataset, only 22.8% (n=58 of 228) of the subjects had calculated CrCl without depending on imputation of at least one covariate. As a representative, the distributions of age, body weight, SCR, and sex are shown in [Figure 3](#) and [Figure 4](#). The covariate prediction model adopted a parametric procedure (i.e., assumption of normality), and using age covariate as an example, the model predicted a higher density for the younger age group. Available literature has demonstrated that uUTI is most common in the young and the elderly, and the prevalence of uUTI increases with age, and particularly, in those over 65 years of age (20% versus 11% in the overall population) as observed by Medina and Castillo-Pino ([Flores-Mireles et al. 2015](#); [Suskind et al. 2016](#); [Medina and Castillo-Pino 2019](#)). Whether the age distribution based on imputation reflects those of the uUTI population in current clinical care remains unclear. Another important covariate consideration is SCR, and the prediction of this covariate was also conducted in the form of parametric procedure. Available SCR data came from 68 individuals (29.8% of final dataset) with a range of 0.7 to 15.8 mg/dL (i.e., skewed to the right). Notably, those with relatively high SCR values were categorized as renal impairment by the Applicant, and because of the presence of numerically high SCR values, subjects with missing SCR were assigned (i.e., imputation from covariate prediction model) relatively high SCR values based on the assumed normal distribution and correlation of covariates from available data, resulting in a "flatter" density for the distribution of all observed and imputed SCR values. As a result, whether the SCR distribution based on imputation reflects those of the uUTI population in current clinical care remains unclear. Another concern is regarding the number of male subjects included in the clinical studies because UTI in male is considered complicated, and the efficacy reanalysis of this submission excludes male subjects (see Sections [6](#) Efficacy). A considerable proportion of male subjects, however, were included in the final PK dataset (including the imputed "male" likelihood being assigned to subjects with missing sex covariate).

When considering subjects without any missing covariates (n=43, as shown in [Table 73](#)), they only account for 18.9% of the total population in the final PK dataset. As such, only a subset of subjects contributed to the correlation between the available covariates and the associated covariate distributions for the covariate prediction model. Ultimately, whether this subset of subjects with available data can reflect the clinically relevant uUTI subject population remains a

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potential concern. In other words, it is uncertain whether the PopPK model parameters (point estimates) and the associated variabilities using the final imputed PK dataset would be representative and whether covariate impacts can be truly assessed in the setting of large proportion of missing covariates.

Table 69. Summary of Studies Included in the PopPK and PK/PD Analyses

Study Identifier	Type	N	Route and Dose (mg)	Population
01 LEO Pharma	Bioavailability tablets vs capsules	19	PO 400 pivmecillinam	healthy volunteers (HVs)
02 Bornemann et al., 1985, N2756A	Bioavailability, food effect	18	PO 400 pivmecillinam	HVs
03 Bornemann et al., 1985, N2757A	Bioavailability and bioequivalence	18	PO 400 pivmecillinam	HVs
05 Damsgaard et al., 1975	Absorption in patients	11	PO 600 pivmecillinam	Patients with urinary tract infections
06 Denneberg et al., 1975	Absorption in patients	20	PO 450 pivmecillinam	Patients with varying degree of kidney function or dialysis
07 Gustafson et al., 1980, 34843	Bioavailability	36	PO 400 pivmecillinam	HVs
09 Holazo et al., 1981	PK and Bioavailability	12	PO 366/733 pivmecillinam and IV 500 mecillinam	HVs
10 LEO Pharma, 1977	Absorption, food effect	9	PO 200 pivmecillinam	HVs
12 Roholt, 1980	Bioavailability	10	PO 400 pivmecillinam	HVs
15 Svarva & Wessel-Aas, 1980	Pharmacokinetics	12	IV 400 mecillinam	Patients with severe renal insufficiency
16 Patel et al., 1979	Pharmacokinetics	13	IV 15 mg/kg mecillinam	Healthy subjects and patients with renal impairment
17 Duvauchelle et al., 1999,	Bioavailability	18	PO 200 and 400 mg pivmecillinam	HVs
18 Bukh, 1982	Pharmacokinetics	13	IV 200, 400, 800, 1200 mecillinam	HVs
19 Holazo, 1981	Pharmacokinetics	12	IV 10 mg/kg mecillinam every 4 hours for 6 doses	HVs
20 Kahlmeter, 1977	Pharmacokinetics	12	IV 300-1000 mg mecillinam 4 times daily	Patients with gram-negative infection or typhoid, paratyphoid fever

Source: Applicant's PopPK report, Table 1, page 24

Abbreviations: HV, healthy volunteer; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; PO, oral; PopPK, population pharmacokinetics

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Table 70. Summary of Demographics for the Full PK Dataset (Including Imputations)

	Healthy (N=172)	Infection (N=23)	Renal Impairment (N=33)	Overall (N=228)
AGE, years				
Mean (SD)	29.4 (9.47)	61.2 (16.5)	54.7 (13.3)	39.3 (17.8)
Median [Min, Max]	26.0 [19.0, 58.0]	63.5 [20.0, 84.0]	55.5 [23.0, 82.0]	33.0 [19.0, 84.0]
Missing	74 (43.0%)	1 (4.3%)	1 (3.0%)	76 (33.3%)
AGE*, years				
Mean (SD)	28.1 (7.28)	60.8 (16.2)	54.6 (13.1)	35.2 (15.8)
Median [Min, Max]	26.4 [19.0, 58.0]	63.0 [20.0, 84.0]	55.0 [23.0, 82.0]	26.4 [19.0, 84.0]
SEX				
Male	32 (18.6%)	10 (43.5%)	11 (33.3%)	53 (23.2%)
Female	92 (53.5%)	13 (56.5%)	22 (66.7%)	127 (55.7%)
Missing	48 (27.9%)	0 (0%)	0 (0%)	48 (21.1%)
SEX*				
Male	32 (18.6%)	10 (43.5%)	11 (33.3%)	53 (23.2%)
0.3 Male Ratio	10 (5.8%)	0 (0%)	0 (0%)	10 (4.4%)
0.4 Male Ratio	10 (5.8%)	0 (0%)	0 (0%)	10 (4.4%)
0.77 Male Ratio	28 (16.3%)	0 (0%)	0 (0%)	28 (12.3%)
Female	92 (53.5%)	13 (56.5%)	22 (66.7%)	127 (55.7%)
BODY WEIGHT, kg				
Mean (SD)	72.0 (11.6)	74.3 (17.7)	70.3 (15.8)	72.1 (12.5)
Median [Min, Max]	70.5 [44.0, 101]	75.0 [45.0, 105]	76.7 [49.6, 84.1]	70.8 [44.0, 105]
Missing	74 (43.0%)	11 (47.8%)	27 (81.8%)	112 (49.1%)
BODY WEIGHT*, kg				
Mean (SD)	72.1 (8.94)	72.3 (13.3)	71.5 (7.77)	72.0 (9.26)
Median [Min, Max]	72.5 [44.0, 101]	75.0 [45.0, 105]	75.0 [49.6, 84.1]	72.5 [44.0, 105]
SERUM CREATININE, mg/dL				
Mean (SD)	1.18 (0.138)	1.19 (0.326)	4.58 (4.37)	2.43 (3.09)
Median [Min, Max]	1.16 [0.915, 1.50]	1.21 [0.735, 1.81]	2.86 [0.994, 15.8]	1.24 [0.735, 15.8]
Missing	141 (82.0%)	11 (47.8%)	8 (24.2%)	160 (70.2%)
SERUM CREATININE*, mg/dL				
Mean (SD)	1.13 (0.0564)	1.14 (0.225)	4.29 (3.69)	1.59 (1.78)
Median [Min, Max]	1.13 [0.891, 1.46]	1.13 [0.715, 1.76]	3.76 [0.968, 15.4]	1.13 [0.715, 15.4]
CREATININE CLEARANCE, mL/min				
Mean (SD)	88.8 (23.0)	72.3 (20.8)	8.43 (5.11)	71.1 (36.0)
Median [Min, Max]	86.4 [45.8, 143]	70.1 [29.2, 108]	7.60 [0.250, 16.0]	76.5 [0.250, 143]
Missing	141 (82.0%)	11 (47.8%)	24 (72.7%)	176 (77.2%)
CRCL*, mL/min				
Mean (SD)	93.2 (16.2)	64.4 (18.5)	34.5 (33.7)	81.8 (29.1)
Median [Min, Max]	95.1 [45.8, 166]	62.8 [29.2, 108]	18.9 [0.250, 113]	89.6 [0.250, 166]
ADMINISTRATION ROUTE				
IV	32 (18.6%)	12 (52.2%)	18 (54.5%)	62 (27.2%)
PO	140 (81.4%)	11 (47.8%)	15 (45.5%)	166 (72.8%)
PRANDIAL STATE				
Unspecified	12 (7.0%)	23 (100%)	27 (81.8%)	62 (27.2%)
Fasted	160 (93.0%)	0 (0%)	6 (18.2%)	166 (72.8%)
Fed	0 (0%)	0 (0%)	0 (0%)	0 (0%)
RACE				
White	79 (45.9%)	0 (0%)	5 (15.2%)	84 (36.8%)
Asian	1 (0.6%)	0 (0%)	0 (0%)	1 (0.4%)
Black	3 (1.7%)	0 (0%)	1 (3.0%)	4 (1.8%)
American Indian	2 (1.2%)	0 (0%)	0 (0%)	2 (0.9%)
Missing	87 (50.6%)	23 (100%)	27 (81.8%)	137 (60.1%)
PK SPECIMEN				
Serum	51 (29.7%)	23 (100%)	27 (81.8%)	101 (44.3%)
Plasma	121 (70.3%)	0 (0%)	6 (18.2%)	127 (55.7%)

Source: Reviewer's analysis based on Applicant's PopPK dataset

Note: Sex was treated as a continuous variable to denote the proportion of males

* Actual and imputed values were included

Abbreviations: CrCl, creatinine clearance derived from Cockcroft-Gault formula; IV, intravenous; N, number of subjects in treatment arm; PK, pharmacokinetic; PO, oral; SD, standard deviation

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Table 71. LLOQ of PK Data by Study

Study Identifier	PK Matrix	LLOQ Plasma ($\mu\text{g/mL}$)	LLOQ Urine ($\mu\text{g/mL}$)	Comment
01 LEO Pharma	Serum	0.1*	UU	Lowest concentration is 0.11 $\mu\text{g/mL}$
02 Bornemann et al., 1985, N2756A	Plasma	0.5	20	Assay limit of sensitivity reported
03 Bornemann et al., 1985, N2757A	Plasma	0.5	20	Assay limit of sensitivity reported
05 Damsgaard et al., 1975	Serum	0.02*	NC	Samples with <0.02 but also 0.01 $\mu\text{g/mL}$
06 Denneberg et al., 1975	Serum	0.05*	UU	Samples with <0.05, <0.06, <0.07, <0.14 $\mu\text{g/mL}$
07 Gustafson et al., 1980, 34843	Plasma	0.5*	25	Samples <0.5 $\mu\text{g/mL}$ flagged as extrapolated.
09 Holazo et al., 1981	Plasma	0.5*	UU	Samples <0.5 $\mu\text{g/mL}$ flagged as extrapolated.
10 LEO Pharma, 1977	Serum	0.04*	UU	Lowest concentration is 0.04 $\mu\text{g/mL}$
12 Roholt, 1980	Serum	0.05*	UU	Lowest concentration is 0.05 $\mu\text{g/mL}$
15 Svarva & Wessel-Aas, 1980	Serum	0.5*	NC	All concentrations above 5 $\mu\text{g/mL}$
16 Patel et al., 1979	Plasma	0.1	NC	Assay limit of sensitivity reported
17 Duvauchelle et al., 1999	Plasma	0.1	10	Assay limit of quantification reported
18 Bukh, 1982	Serum	0.05*	UU	Lowest concentration is 0.06 $\mu\text{g/mL}$
19 Holazo, 1981	Plasma	0.01*	UU	Lowest concentration is 0.01 $\mu\text{g/mL}$
20 Kahlmeter, 1977	Serum	0.4*	NC	Some concentration <0.4 $\mu\text{g/mL}$, but also 0.2 $\mu\text{g/mL}$ reported

*: Assumed LLOQ based on lowest reported data in a certain study or 0.5 $\mu\text{g/mL}$ if unknown; UU: unknown - urine reported as amount excreted; NC: No urine collection in this study.

Source: Applicant's PopPK report, Table 8, page 36

Abbreviations: LLOQ, lower limit of quantitation; NC, no collection; PK, pharmacokinetic; PopPK, population pharmacokinetic; UU, unknown

Table 72. Summary of Missing Covariates by Study

	STUDY	AGE	WT	SEX	RACE	SCR	CRCL
	01 LEO Pharma	100%	100%	100%	100%	100%	100%
	02 Bornemann et al., 1985, N2756A	-	-	-	-	100%	100%
	03 Bornemann et al., 1985, N2757A	-	-	-	-	100%	100%
	05 Damsgaard et al., 1975	9.1%	100%	-	100%	100%	100%
	06 Denneberg et al., 1975	6.7%	100%	-	100%	-	100%
	07 Gustafson et al., 1980, 34843	100%	100%	27.8%	100%	100%	100%
	09 Holazo et al., 1981	-	-	-	-	100%	100%
	10 LEO Pharma, 1977	100%	100%	100%	100%	100%	100%
	12 Roholt, 1980	100%	100%	100%	100%	100%	100%
	15 Svarva & Wessel-Aas, 1980	-	100%	-	100%	16.7%	25%
	16 Patel et al., 1979	-	-	-	-	100%	100%
	17 Duvauchelle et al., 1999	-	-	-	-	-	-
	18 Bukh, 1982	-	-	-	100%	-	-
	19 Holazo, 1981	-	-	-	-	100%	100%
	20 Kahlmeter, 1977	-	-	-	100%	-	-

Source: Applicant's PopPK report, Table 9, page 46

Percentages represent percent missing; 100% indicates completely missing

Abbreviations: CRCL, creatinine clearance; PopPK, population pharmacokinetic; SCR, serum creatinine, WT, weight

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Table 73. Summary of Demographics for Subjects Without Any Missing Data

	Healthy (N=31)	Infection (N=12)	Overall (N=43)
AGE, years			
Mean (SD)	33.6 (11.1)	53.8 (17.6)	39.2 (15.9)
Median [Min, Max]	34.0 [19.0, 55.0]	59.0 [20.0, 78.0]	37.0 [19.0, 78.0]
SEX			
Male	9 (29.0%)	5 (41.7%)	14 (32.6%)
Female	22 (71.0%)	7 (58.3%)	29 (67.4%)
BODY WEIGHT, kg			
Mean (SD)	72.7 (13.9)	74.3 (17.7)	73.2 (14.8)
Median [Min, Max]	67.4 [55.4, 101]	75.0 [45.0, 105]	69.2 [45.0, 105]
SERUM CREATININE, mg/dL			
Mean (SD)	1.18 (0.138)	1.19 (0.326)	1.18 (0.204)
Median [Min, Max]	1.16 [0.915, 1.50]	1.21 [0.735, 1.81]	1.18 [0.735, 1.81]
CREATININE CLEARANCE, mL/min			
Mean (SD)	88.8 (23.0)	72.3 (20.8)	84.2 (23.4)
Median [Min, Max]	86.4 [45.8, 143]	70.1 [29.2, 108]	81.3 [29.2, 143]
ADMINISTRATION ROUTE			
IV	13 (41.9%)	12 (100%)	25 (58.1%)
PO	18 (58.1%)	0 (0%)	18 (41.9%)
RACE			
White	17 (54.8%)	0 (0%)	17 (39.5%)
Black	1 (3.2%)	0 (0%)	1 (2.3%)
Missing	13 (41.9%)	12 (100%)	25 (58.1%)
PRANDIAL STATE			
Unspecified	0 (0%)	12 (100%)	12 (27.9%)
Fasted	31 (100%)	0 (0%)	31 (72.1%)
PK SPECIMEN			
Serum	13 (41.9%)	12 (100%)	25 (58.1%)
Plasma	18 (58.1%)	0 (0%)	18 (41.9%)

Source: Reviewer's analysis based on Applicant's PopPK dataset

Abbreviations: IV, intravenous; N, number of subjects in treatment arm; PK, pharmacokinetic; PO, oral; PopPK, population pharmacokinetic; SD, standard deviation

Figure 3. Densities of Continuous Covariates in the Final PK Dataset

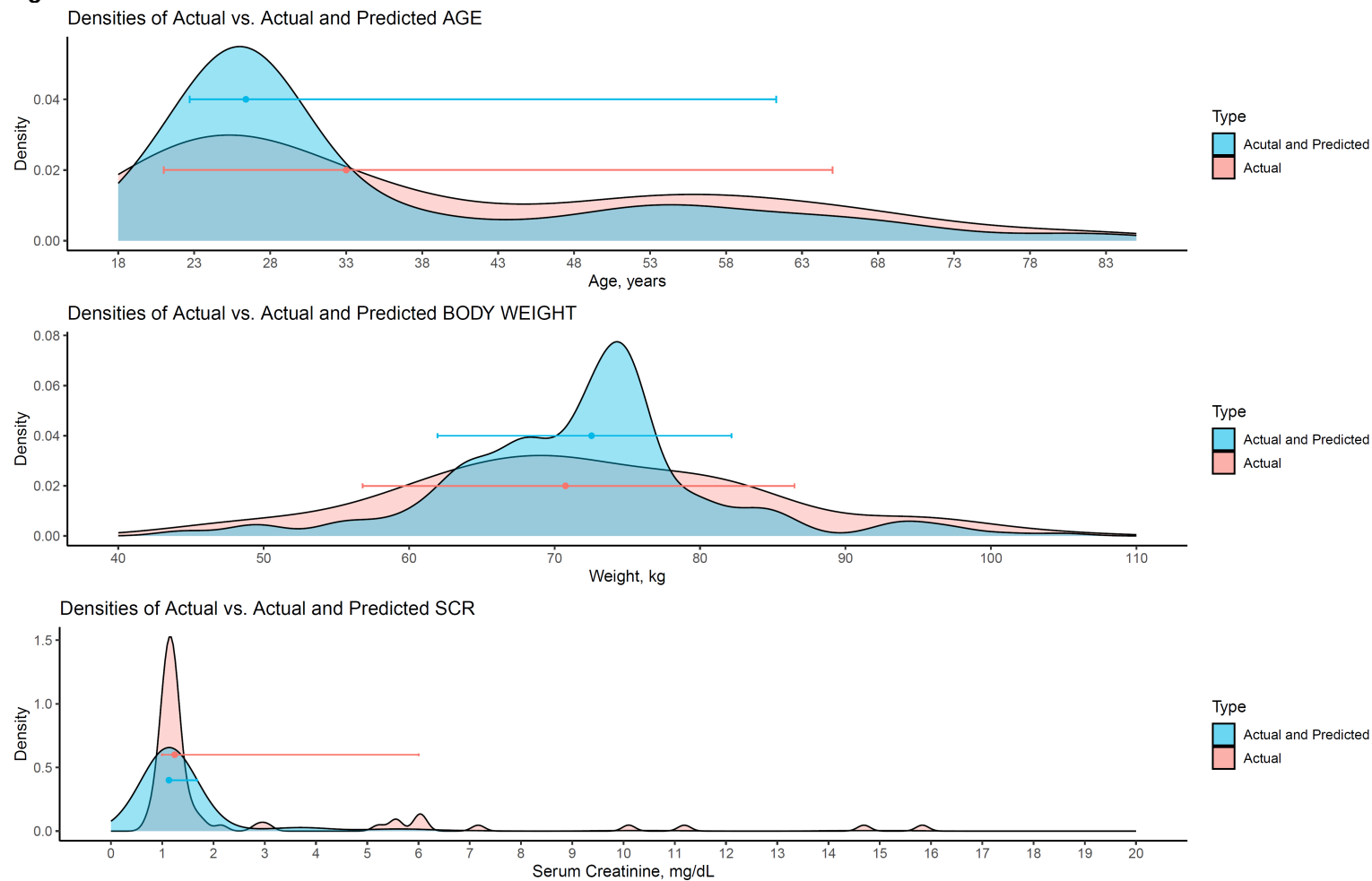
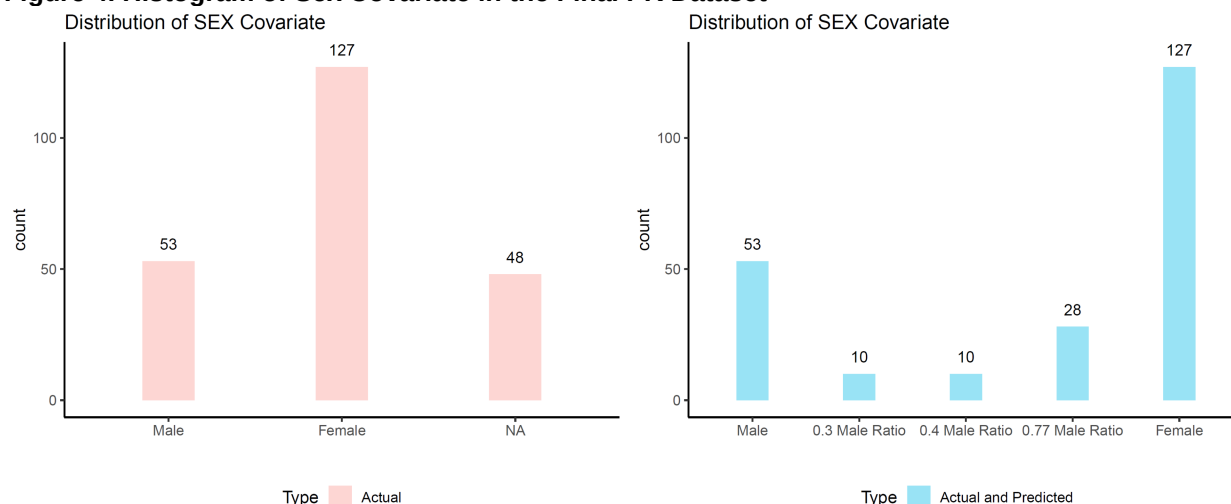


Figure 4. Histogram of Sex Covariate in the Final PK Dataset



Source: Reviewer's analysis based on Applicant's PopPK dataset

Notes: NA denotes missing data; male ratio denotes probability of model predicted sex based on reported percentage of male subjects in individual study report but without reporting subject level data

Abbreviations: NA, not applicable; PK, pharmacokinetic; PopPK, population pharmacokinetic

Covariate Prediction Model

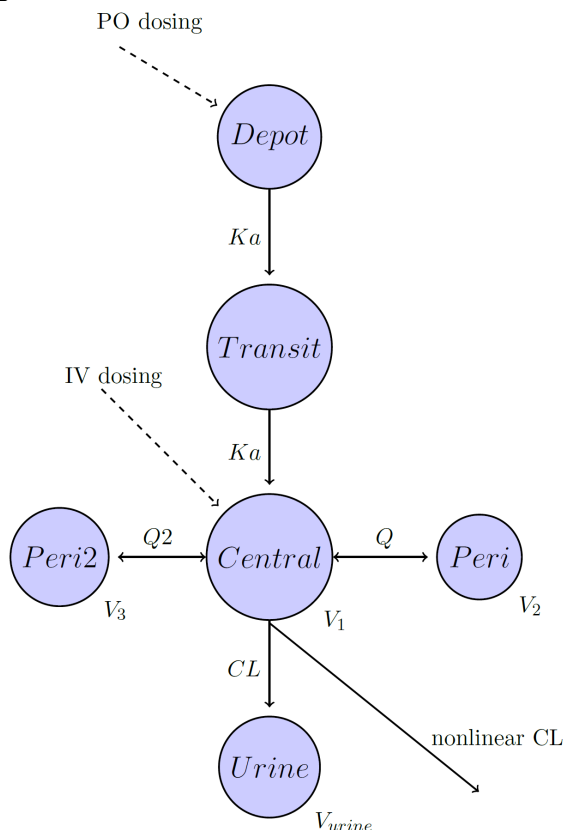
To evaluate covariate impact and assist in PopPK model building, a covariate prediction model was developed to predict the most likely value for the missing subject level data.

Base Model

A two-compartment PopPK model with linear renal clearance (CL) and saturable nonlinear nonrenal CL was previously developed to describe oral PIV and IV MEC disposition in healthy subjects. Lag time, first-order absorption, and saturable transit compartment absorption models were tested to describe oral PIV. Urine data was also modeled during PopPK model development; however, only a single six-hour nominal time after dose urine PK record was available for the subject population. A schematic of the structural model is shown in [Figure 5](#).

Interindividual variability was incorporated assuming a log-normal distribution for subject level random effects. Residual variability was tested as additive, proportional, or both on the dependent variable (for both plasma and urine data). Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value, accuracy of parameter estimation (i.e., 95% CI excluding 0), successful model convergence, and diagnostic plots.

Figure 5. Schematic of Model Structure



Source: Applicant's PopPK report, Figure 10, page 63

Abbreviations: CL, clearance; IV, intravenous; Ka , absorption rate constant; PO, oral; PopPK, population pharmacokinetic; Q , intercompartmental flow; $Q2$, intercompartmental flow; V_1 , central volume of distribution; V_2 , peripheral volume of distribution; V_3 , peripheral volume of distribution; V_{urine} , urine compartment

Covariate Analysis

Because of the large proportions of missing covariates, a formal covariate analysis was not undertaken. Instead, subject level ETAs (model-derived) were graphically examined against covariate values to guide inclusion of covariate effects.

14.5.4. Final Model

Covariate Prediction Model

The final covariate prediction model is summarized in [Table 74](#).

Table 74. Parameter Estimates of the Prediction Model for Missing Covariates

Parameter	Description	Estimate	95% CI
θ_1	Mean weight (<i>kg</i>)	64.1	(60.7 - 67.8)
θ_2	Mean sex	0.772	(0.698 - 0.832)
θ_3	Mean age (years)	26.4	(25.0 - 27.8)
θ_4	Mean serum creatinine ($\mu\text{mol/L}$)	103	(97.8 - 108)
θ_5	Increase in Male weight as percentage of female (%)	16.9	(10.9 - 26.4)
θ_6	RI and Infection patients age (years)	51.9	(48.3 - 55.7)
θ_7	Infection patients sex	0.472	(0.317 - 0.633)
θ_8	Mean serum creatinine RI patients ($\mu\text{mol/L}$)	342	(236 - 496)
$\omega_{1,1}^2$	IIV, WT var (CV%)	0.0248 (15.8)	(0.0185 - 0.0311)
$\omega_{3,3}^2$	IIV, Age var (CV%)	0.0744 (27.8)	(0.0547 - 0.0941)
$\omega_{4,4}^2$	IIV, Serum creatinine var (CV%)	0.0241 (15.6)	(0.00834 - 0.0398)
$\omega_{5,5}^2$	IIV, Serum creatine RI patients var (CV%)	1.08 (139.5)	(0.817 - 1.34)
$\sigma_{1,1}$	Proportional Residual Variability WT (CV%)	0.0003 (1.8)	(0.000168 - 0.000491)
$\sigma_{3,3}$	Proportional Residual Variability age (CV%)	0.0017 (4.1)	(0.00134 - 0.00205)
$\sigma_{4,4}$	Proportional Residual Variability serum creatinine (CV%)	0.0044 (6.7)	(0.000664 - 0.00820)

Parameter values for the structural PopPK model. ω_X^2 : variance of the IIV of parameter X, IIV as a % CV is derived from variance according to $\sqrt{e^{\omega_X^2}} - 1 \cdot 100$. NC: Not calculated (fixed). $\omega_{X,Y}^2$: covariance of the IIV of parameters X and Y.

Source: Applicant's PopPK report, Table 11, page 50

Abbreviations: CI, confidence interval; CV%, coefficient of variation expressed as a percentage; IIV, interindividual variability; NC, not calculated; PopPK, population pharmacokinetic; RI, renal impairment; WT, body weight

Considering the limitations of the dataset, the FDA pharmacometric review team's interpretation of the parameter estimates in a clinical context may be unclear based on available data. The parameter estimates are provided for completeness. For more information, refer to the Applicant's PopPK report in Section [5.2 Clinical Pharmacology/Pharmacokinetics](#).

Final PopPK Model

The PopPK analysis was conducted in several steps by the Applicant. First, a structural model was developed using the MEC PK data in plasma, serum, and urine obtained in healthy volunteers receiving MEC after single- or multiple-dose IV administration. Subsequently, the MEC PK data obtained after oral administration of several PIV formulations under various prandial conditions were appended to allow estimation of the oral bioavailability of PIV and to develop the absorption model. Lastly, MEC PK data obtained in subjects with infections or with severe renal impairment were appended to identify the impact of diseases on PK.

The final model was a two-compartment distribution model with first-order renal elimination and nonlinear nonrenal elimination, and only the renal elimination goes into the urine compartment. For the oral formulation of PIV, the absorption phase was described with a single transit compartment. The residual variability model included a proportional error term for the plasma data and a combined additive and proportional error terms for the urine data. The parameter estimates for the final covariate model are listed in [Table 75](#). The goodness-of-fit and conditional weighted residual plots are shown in [Figure 6](#) and [Figure 7](#), respectively. A forest plot of covariate impact on AUC is shown in [Figure 8](#). Additional diagnostic plots are detailed in Section 5.4 of the Applicant's PopPK report.

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Table 75. Parameter Estimates (RSE) and Median (95% CI) for the Final PopPK Model

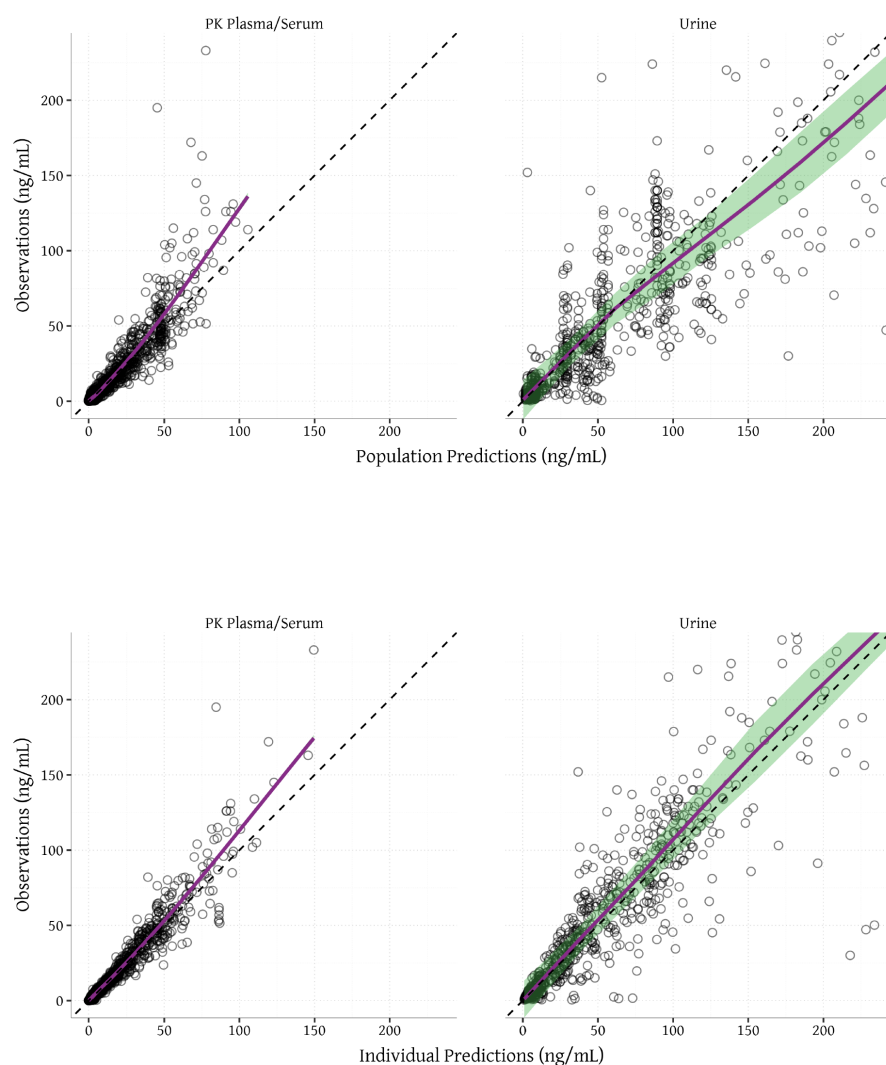
Parameter	Description	Units	Estimate	Estimated/Fixed	Bootstrap Estimate	Bootstrap 95% CI
θ_1	Renal Clearance	L/h	10.9	estimated	11	(10.4 - 11.4)
θ_2	Central Volume	L	11.7	estimated	11.6	(10.1 - 13)
θ_3	Inter-compartmental Clearance	L/h	7.24	estimated	7.61	(5.88 - 8.97)
θ_4	Peripheral Volume	L	11.6	estimated	11.8	(10.1 - 13.6)
θ_5	Second Inter-compartmental Clearance	L/h	6.07	estimated	6.03	(1.92 - 11.1)
θ_6	Second Peripheral Volume	L	1.87	estimated	1.64	(0.432 - 3.15)
θ_7	Maximum Nonrenal Clearance	mg/h	187	estimated	195	(131 - 318)
θ_8	Amount of half max nonrenal Clearance	mg	231	estimated	236	(135 - 453)
θ_9	Absorption Rate	/h	1.67	estimated	1.66	(1.55 - 1.76)
θ_{10}	Bioavailability	-	0.65	estimated	0.651	(0.601 - 0.712)
θ_{11}	Power dose effect F1	-	-1.57	estimated	-1.56	(-2.28 - -1.1)
θ_{12}	Change in Ka Solution or Suspension	-	1.13	estimated	1.13	(1.04 - 1.22)
θ_{13}	Change in Ka Capsules	-	0.827	estimated	0.831	(0.732 - 0.923)
θ_{14}	Change in Ka forms 5 and 6	-	1.38	estimated	1.39	(1.22 - 1.56)
θ_{15}	Food effect on F1	-	0.838	estimated	0.847	(0.524 - 1.07)
θ_{16}	Food effect on Ka	-	0.858	estimated	0.864	(0.773 - 0.975)
θ_{17}	Power CRCL effect on CL	-	0.681	estimated	0.719	(0.527 - 1.22)
θ_{18}	Severe RI effect on KM	-	5.82	estimated	5.18	(2.46 - 26.7)
$\omega_{1,1}^2$	IIV, Clearance	var (CV%)	0.0956 (31.7)	estimated	0.0955	(0.0707 - 0.133)
$\omega_{2,2}^2$	IIV, Central Volume	var (CV%)	0.147 (39.8)	estimated	0.127	(0.0565 - 0.257)
$\omega_{4,4}^2$	IIV, Peripheral Volume	var (CV%)	0.184 (44.9)	estimated	0.183	(0.114 - 0.305)
$\omega_{8,8}^2$	IIV, KM	var (CV%)	0.248 (53.1)	estimated	0.209	(0.106 - 0.361)
$\omega_{9,9}^2$	IIV, absorption rate	var (CV%)	0.0754 (28)	estimated	0.0699	(0.0487 - 0.102)
$\omega_{10,1}^2$	IIV, Bioavailability	var (CV%)	0.417 (71.9)	estimated	0.378	(0.21 - 0.674)
$\sigma_{1,1}$	Proportional Residual Variability PK	var	0.0668	estimated	0.0666	(0.0613 - 0.0734)
$\sigma_{3,3}$	Proportional Residual Variability Urine	var	0.177	estimated	0.167	(0.134 - 0.219)
$\sigma_{4,4}$	Additive Residual Variability Urine	var $\mu\text{g/mL}$	0.0799	estimated	0.136	(0.00044 - 1.61)

Source: Applicant's PopPK report, Table 18, page 64

Note: Parameter estimates are presented as non-transformed or back-calculated values, with respect to the log- and logit-transformed parameterizations; standard reference weight of 70 kg was used in allometric scaling for all relevant parameters with fixed exponents of 0.75 for clearance and 1 for clearance and volume related terms, respectively.

Abbreviations: CI, confidence interval; CL, clearance; CRCL, creatinine clearance; IIV, interindividual variability; F1, bioavailability; Ka, absorption rate constant; KM, Michaelis constant; PK, pharmacokinetic; PopPK, population pharmacokinetic; RSE, relative standard error

Figure 6. Goodness-of-Fit Plots for the Final PopPK Model

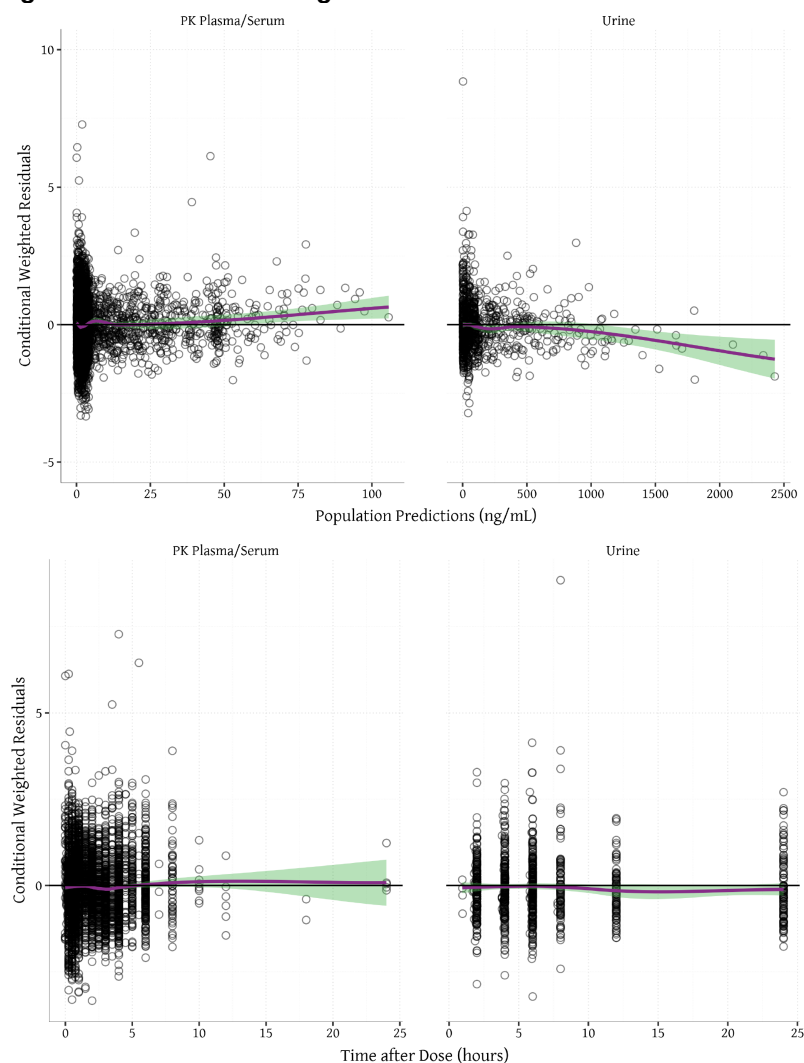


Source: Applicant's PopPK report, Figure 11, page 65

Notes: Solid line, LOESS smooth fit; shaded area, 95% confidence interval of LOESS; dashed line, line of unity

Abbreviations: LOESS, locally estimated scatterplot smoothing; PK, pharmacokinetic; PopPK, population pharmacokinetic

Figure 7. Conditional Weighted Residuals Plots

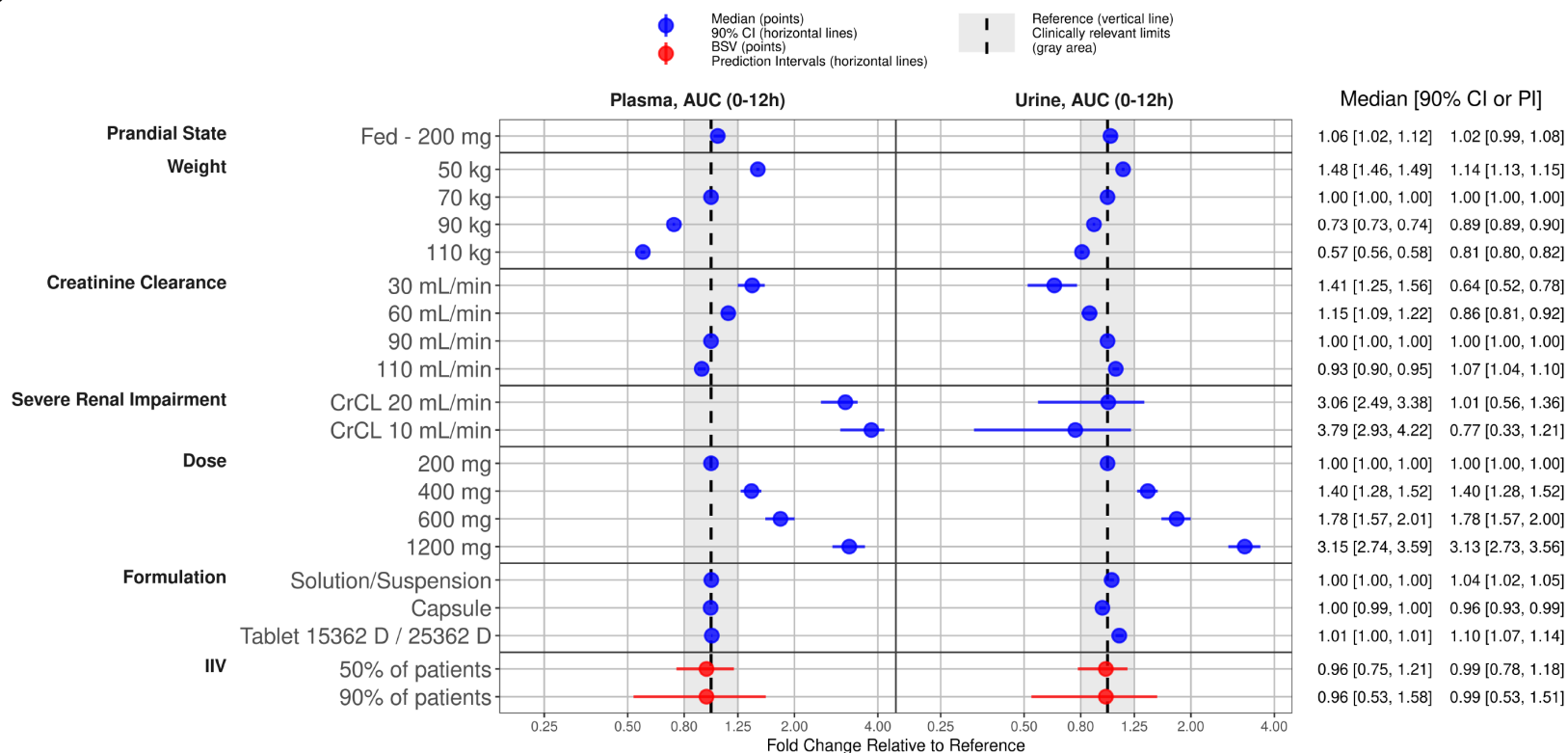


Source: Applicant's PopPK report, Figures 12 and 13, page 66-67

Note: Solid line, LOESS smooth fit; shaded area, 95% confidence interval of LOESS

Abbreviations: LOESS, locally estimated scatterplot smoothing; PK, pharmacokinetic; PopPK, population pharmacokinetic

Figure 8. Forest Plot of Covariate Effect on AUC in Plasma and Urine



Source: Applicant's PopPK report, Figure 27, page 81

Note: Reference subject covariates: 200 mg PIV dose (equivalent to 137 mg mecillinam) of the tablet formulation, administered under fasted conditions to a healthy individual with CrCL of 90 mL/min

Abbreviations: AUC, area under the concentration-time curve; BSV, between subject variability; CI, confidence interval; CrCL, creatinine clearance; IIV, interindividual variability; PI, prediction interval

Given the various issues discussed above regarding the PK dataset, the application of the final PopPK model is limited. Nevertheless, the model development and results are included for completeness. The FDA reviewer noted an additional concern with the PopPK model structure. The final PopPK model was parameterized with total CL, including nonlinear nonrenal and linear renal clearance, from the central volume of distribution. The nonrenal component is a saturable function (i.e., Michaelis-Menten kinetics) with the Km parameter describing the half maximal nonrenal clearance; however, Km is numerically increased by more than five-fold (i.e., parameter point estimate) when renal impairment (defined as CL_{CR} <30 mL/min) classification is present. Therefore, both the renal

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and nonrenal CL (as a result of K_m increase in the denominator) are expected to decrease numerically when a subject is considered renally impaired. The physiological and mechanistic basis, as well as clinical relevance, of this modeled relationship is unclear. Overall, the PK dataset and the utility of the PopPK model are limited and preclude the assessment of the simulation and PTA analysis results, which may not be readily generalizable for the indication and uUTI subject population.

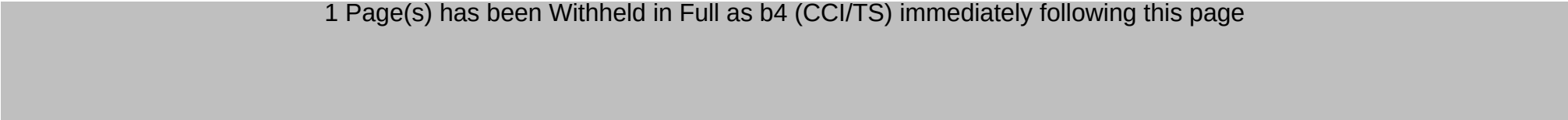
14.5.5. Probability of Target Attainment

Results of the PTA analysis is described here for completeness.

(b) (4)



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14.6. Pharmacogenetics

Not applicable.

15. Study / Trial Design

Not applicable.

16. Efficacy

Efficacy for Supportive Studies

The Hansen and Bresky studies were submitted as supportive efficacy studies but were not reviewed in detail for the evaluation of efficacy because the Hansen study did not have a randomized comparator arm and the Bresky study had a very small number of subjects and did not have efficacy evaluations of clinical cure and overall response.

In the Applicant's reanalysis of the Hansen study, which was conducted similarly to the Ferry, Munday, Vik, and Nicolle studies discussed in Section 6 Efficacy (Evaluation of Benefit), microbiological cure at test-of-cure (TOC) was 84% and microbiological success in subjects with *E. coli* infections was 85%. Section 5.2.2 of the integrated summary of effectiveness (ISE) stated that clinical cure (not defined in the publication) was found in 80 to 90% of subjects in the 3-day and 7-day treatment groups.

Microbiological cure at TOC was 50% in the pivmecillinam 200 mg TID for 10 days arm compared to 48% in the amoxicillin 375 mg TID in the Bresky study. Microbiological success in subjects with *E. coli* infections was 40% in the pivmecillinam 200 mg TID for 10 days arm in the Bresky study compared to 50% in the amoxicillin 375 mg TID for 10 days arm. See [Table 78](#) for details.

Table 78. Applicant's Reanalysis, Micro-ITT Analysis Set, Hansen 1981 and Bresky 1977 Studies

Endpoint	Hansen (1981)	Bresky (1977)	
	Pivmecillinam 200 mg TID x 7 Days N=106	Pivmecillinam 200 mg TID x 10 Days N=18	Amoxicillin 375 mg TID x 10 Days N=21
Microbiological cure at TOC n (%)	89 (84)	9 (50)	10 (47.6)
Microbiological success versus <i>E. coli</i> n/N1 (%)	75/88 (85.2)	6/15 (40)	8/16 (50)

Source: Table 21 in the ISE; ([Bresky 1977](#); [Hansen et al. 1981](#))

Abbreviations: ITT, intent-to-treat; micro-ITT, microbiological intent-to-treat; N, number of subjects in the micro-ITT analysis set; n, number of subjects with microbiological success at TOC visit; N1, number of subjects with specified baseline pathogen; % = n/N1 x 100; TID, three times daily; TOC, test-of-cure visit

Additional Primary Efficacy Analysis

Table 79. Demographic Characteristics, ITT Analysis Set, Primary Efficacy Studies

Parameters	Menday 2000		Vik 2018		Ferry 2007	
	Pivmecillinam 200mg TID × 3 Days N=207	Cephalexin 250mg QID × 7 Days N=208	Pivmecillinam 200mg TID × 3 Days N=170	Ibuprofen 600mg TID × 3 Days N=169	Pivmecillinam 200mg TID × 7 Days N=192	Placebo N=201
Age (years)						
N	207	208	170	169	192	201
Mean (std)	30.6 (15.70)	31.3 (16.16)	28.2 (9.94)	27.9 (8.51)	44.7 (18.27)	42.8 (17.76)
Median	24	24	25	25	44	41
Min, Max	18, 85	18, 87	18, 59	18, 58	18, 82	18, 83
≤24 years	104 (50.2)	109 (52.4)	84 (49.4)	77 (45.6)	37 (19.3)	44 (21.9)
25 - <50 years	79 (38.2)	72 (34.6)	75 (44.1)	85 (50.3)	77 (40.1)	87 (43.3)
≥50 years	24 (11.6)	27 (13)	11 (6.5)	7 (4.1)	78 (40.6)	70 (34.8)
≤65 years	189 (91.3)	192 (92.3)	170 (100)	169 (100)	157 (81.8)	173 (86.1)
>65 years	18 (8.7)	16 (7.7)	0 (0)	0 (0)	35 (18.2)	28 (13.9)

Source: Table 1.3.1.1.1 of the ISE; ([Menday 2000](#); [Ferry et al. 2007](#); [Vik et al. 2018](#))

Notes: Percentages are calculated as n/N x 100

Abbreviations: ITT, intent-to-treat; max, maximum; min, minimum; N, number of subjects in the ITT analysis set; n, number of subjects in the specified category; std, standard deviation.

Table 80. Analysis Populations and Analysis Sets, Primary Efficacy Studies

	Ferry (2007)		Menday (2000)		Vik (2018)	
	<u>Pivmecillinam</u> 200 mg TID x 7 days n (%)	Placebo n (%)	<u>Pivmecillinam</u> 200 mg TID x 3 days n (%)	Cephalexin 250 mg QID x 7 days n (%)	<u>Pivmecillinam</u> 200 mg TID x 3 days n (%)	Ibuprofen 600 mg TID x 3 days n (%)
Overall						
Randomized Subjects [1]	287	291	219	222	189	194
Efficacy Population [2]	192 (66.9)	201 (69.1)	207 (94.5)	208 (93.7)	170 (89.9)	169 (87.1)
Reason for exclusion						
Male or Female years <18	0 (0.0)	1 (0.3)	6 (2.7)	3 (1.4)	0 (0.0)	0 (0.0)
No evidence of pyuria	82 (28.6)	69 (23.7)	N/A	N/A	14 (7.4)	21 (10.8)
Did not have 2 symptoms [3]	22 (7.7)	22 (7.6)	7 (3.2)	12 (5.4)	1 (0.5)	3 (1.5)
Signs of complicated UTI	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.2)	2 (1.0)
ITT Analysis Set [2]	192 (66.9)	201 (69.1)	207 (94.5)	208 (93.7)	170 (89.9)	169 (87.1)
Micro-ITT Analysis Set	137 (71.4)	134 (66.7)	127 (61.4)	132 (63.5)	105 (61.8)	119 (70.4)
No positive urine culture	55 (28.6)	67 (33.3)	74 (35.7)	59 (28.4)	65 (38.2)	50 (29.6)
Pathogen non-susceptible to comparator*	N/A	N/A	6 (2.9)	17 (8.2)	N/A	N/A
Expanded Micro-ITT Analysis Set	137 (71.4)	134 (66.7)	133 (64.3)	149 (71.6)	105 (61.8)	119 (70.4)

Source: Table 13 of the ISE; ([Menday 2000](#); [Ferry et al. 2007](#); [Vik et al. 2018](#))

* Not assessed in Ferry study given comparator of placebo or Vik study given comparator of ibuprofen.

[1] Randomized subjects are those enrolled in the studies based on each study's inclusion/exclusion criteria and assigned to study drug.

[2] Percentages are calculated based on the randomized subjects.

[3] Symptoms include dysuria, frequency, urinary urgency, and suprapubic pain (or loin pain, abdominal pain as determined appropriate by Sponsor review).

Percentages for the micro-ITT and expanded micro-ITT analysis sets are based on the ITT analysis set.

Abbreviations: ITT, intent-to-treat; micro-ITT, microbiological intent-to-treat; N, number of subjects in the specified category; N/A, not applicable; QID, four times daily; TID, three times daily; UTI, urinary tract infection

Duration of Therapy (3 versus 7 Days)

Assessment

Assessments of efficacy endpoints in the three primary efficacy studies for the 200 mg dose of pivmecillinam were performed after 3 to 7 days of treatment depending on the study but there was only one duration for this dose within each study (e.g., pivmecillinam 200 mg BID and TID for 7 days in the Ferry study). In the Ferry study pivmecillinam 400 mg BID treatment for 3 days had the lowest overall, clinical and microbiological responses compared to the 200 mg dose arms where treatment was for 7 days. Overall responses were 59% for the pivmecillinam 200 mg BID for 7 days arm, 62% for the pivmecillinam 200 mg TID for 7 days arm and 46% for the pivmecillinam 400 mg BID for 3 days arm. The difference between the overall response in the pivmecillinam 200 mg BID for 7 days and pivmecillinam 400 mg BID for 3 days regimen was nominally statistically significant ($p=0.039$) as was the difference between the overall response in the pivmecillinam 200 mg TID for 7 days and pivmecillinam 400 mg BID for 3 days regimen ($p=0.011$), suggesting that 7 days of treatment may have better efficacy. There appeared to be little difference in response rates between BID and TID regimens for the 200 mg dose ($p=0.71$), which further supported the duration of treatment (rather than BID versus TID regimen or dose) as the underlying factor for improved response. See [Table 81](#) for details.

Table 81. Overall Responses in the Reanalysis, Micro-ITT Analysis Set, Ferry 2007 Study

Categories	Pivmecillinam 200 mg BID × 7 Days	Pivmecillinam 200 mg TID × 7 Days	Pivmecillinam 400 mg BID × 3 Days	Placebo
Success n/N (%)	82/138 (59.4%)	85/137 (62%)	62/134 (46.3%)	14/134 (10.4%)
Risk difference	49%	51.6%	35.8%	
95% CI for RD	38.5%, 59.4%	41.2%, 62%	25.2%, 46.5%	
p-Value	<0.001	<0.001	<0.001	

Source: Table 17 in the ISE; ([Ferry et al. 2007](#))

Note: Risk differences for success rates of pivmecillinam-placebo

Abbreviation: BID, twice daily; CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the microbiological ITT analysis set; n, number of subjects in the specified category; RD, risk difference; TID, three times daily

Overall response for the 3 days regimen of the 200 mg TID regimen of pivmecillinam was 72% in the Menday study and 66% in the Vik study. Both of these responses were higher than the overall responses in the Ferry study for either 200 mg regimen. In addition, the overall response rate of 56% in the Nicolle study for the 400 mg BID for 3 days regimen was only slightly lower than the 59% overall response observed for the 200 mg BID for 7 days arm in the Ferry study and 10% higher than the 46% overall response observed for the same 400 mg BID for 3 days regimen in the Ferry study. However, these were cross-study comparisons which may have been influenced by different efficacy evaluation criteria and other confounding factors.

Conclusion

Within-study comparisons comparing duration of treatment were only available in the Ferry study where observed responses for the 7-day arm were 13 to 16% higher than those observed for the 3-day arm, suggesting that 7 days of treatment was the optimal duration compared to 3 days. Cross-study comparisons did not appear to support this conclusion, but these are less reliable than within-study comparisons. Cross-study comparisons may differ due to factors like duration of therapy for uUTI which may be based on response to therapy and/or other potential factors that can affect clinical response such as specific antimicrobial used ([Gupta et al. 2011](#)).

Microbiological and clinical successes in the pivmecillinam arms were significantly higher than placebo and ibuprofen arms among the subgroup of subjects with *E. coli* infections in the three primary efficacy studies, as shown in [Table 82](#) and [Table 83](#).

Table 82. Microbiological Success at Test-of-Cure by Baseline Pathogen, Micro-ITT Analysis Set, Primary Efficacy Studies

Baseline Pathogen	Ferry (2007)		Menday (2000)		Vik 2018	
	Pivmecillinam 200 mg TID x 7 Days N=137 n/N1 (%)	Placebo N=134 n/N1 (%)	Pivmecillinam 200 mg TID x 3 Days N=127 n/N1 (%)	Cephalexin 250 mg QID x 7 Days N=132 n/N1 (%)	Pivmecillinam 200 mg TID x 3 Days N=105 n/N1 (%)	Ibuprofen 600 mg TID x 3 Days N=119 n/N1 (%)
Gram-Negative						
Enterobacteriaceae						
<i>Citrobacter koseri</i>	N/A	N/A	N/A	N/A	N/A	0/2 (0)
<i>Citrobacter species</i>	1/1 (100)	2/2 (100)	1/1 (100)	N/A	N/A	N/A
<i>Enterobacter species</i>	1/2 (50)	3/5 (60)	1/1 (100)	1/1 (100)	1/3 (33.3)	2/2 (100)
<i>Escherichia coli</i>	109/121 (90.1)	21/107 (19.6)	82/104 (78.8)	87/107 (81.3)	65/88 (73.9)	52/96 (54.2)
<i>Klebsiella pneumoniae</i>	N/A	N/A	1/4 (25)	2/3 (66.7)	2/2 (100)	0/1 (0)
<i>Klebsiella species</i>	5/6 (83.3)	2/8 (25)	2/2 (100)	1/1 (100)	N/A	N/A
<i>Proteus mirabilis</i>	1/1 (100)	N/A	6/9 (66.7)	8/13 (61.5)	N/A	0/1 (0)
Gram-Positive						
<i>Enterococcus faecalis</i>	N/A	N/A	N/A	N/A	N/A	0/2 (0)
<i>Enterococcus species</i>	1/4 (25)	4/6 (66.7)	N/A	N/A	N/A	N/A
<i>Staphylococcus aureus</i>	1/2 (50)	0/1 (0)	N/A	1/1 (100)	N/A	N/A
<i>Staphylococcus saprophyticus</i>	1/2 (50)	3/6 (50)	4/7 (57.1)	6/6 (100)	10/12 (83.3)	10/15 (66.7)

Source: Table 25 in the ISE; ([Menday 2000](#); [Ferry et al. 2007](#); [Vik et al. 2018](#))

Note: Pathogens listed as Genus "species" did not have the species identified and may include any species including the listed pathogen that has been identified to the species level

Note: Percentages are calculated as n/N1 x 10.

Abbreviations: ITT, intent-to-treat; micro-ITT, microbiological intent-to-treat; N, number of subjects in the Micro-ITT analysis set; n, number of subjects with microbiological success at test-of-cure visit; N1, number of subjects with specified baseline pathogen.; N/A, not applicable; QID, four times daily; TID, three times daily

Table 83. Clinical Cure Rates at Test-of-Cure by Baseline Pathogen, Micro-ITT Analysis Set, Primary Efficacy Studies

Baseline Pathogen	Ferry (2007)		Menday (2000)		Vik 2018	
	Pivmecillinam 200 mg TID x 7 Days N=137 n/N1 (%)	Placebo N=134 n/N1 (%)	Pivmecillinam 200 mg TID x 3 Days N=127 n/N1 (%)	Cephalexin 250 mg QID x 7 Days N=132 n/N1 (%)	Pivmecillinam 200 mg TID x 3 Days N=105 n/N1 (%)	Ibuprofen 600 mg TID x 3 Days N=119 n/N1 (%)
Gram-Negative						
Enterobacteriaceae						
<i>Citrobacter koseri</i>	N/A	N/A	N/A	N/A	N/A	0/2 (0)
<i>Citrobacter species</i>	1/1 (100)	1/2 (0)	1/1 (100)	N/A	N/A	N/A
<i>Enterobacter species</i>	1/2 (50)	2/5 (40)	1/1 (100)	1/1 (100)	2/3 (66.7)	1/2 (50)
<i>Escherichia coli</i>	79/121 (65.3)	23/107 (21.5)	87/104 (83.7)	92/107 (86)	69/88 (78.4)	38/96 (39.6)
<i>Klebsiella pneumoniae</i>	N/A	N/A	3/4 (75)	2/3 (66.7)	1/2 (50)	1/1 (100)
<i>Klebsiella species</i>	3/6 (50)	4/8 (50)	1/2 (50)	0/1 (0)	N/A	N/A
<i>Proteus mirabilis</i>	1/1	N/A	7/9 (77.8)	10/13 (76.9)	N/A	0/1 (0)
Gram-Positive						
<i>Enterococcus faecalis</i>	N/A	N/A	N/A	N/A	N/A	1/2 (50)
<i>Enterococcus species</i>	1/4 (25)	3/6 (50)	N/A	N/A	N/A	N/A
<i>Staphylococcus aureus</i>	1/2 (50)	0/1 (0)	N/A	1/1 (100)	N/A	N/A
<i>Staphylococcus saprophyticus</i>	1/2 (50)	0/6 (0)	5/7 (71.4)	6/6 (100)	9/12 (75)	4/15 (26.7)

Source: Table 28 in the ISE; (Menday 2000; Ferry et al. 2007; Vik et al. 2018)

Note: Percentages are calculated as n/N1 x 100.

Abbreviations: ITT, intent-to-treat; micro-ITT, microbiological intent-to-treat; N, number of subjects in the Micro-ITT analysis set; n, number of subjects with clinical success at test-of-cure visit; N1, number of subjects with specified baseline pathogen; N/A, not applicable; QID, four times daily; TID, three times daily

16.1. Subgroup Analyses

Overall responses in the Ferry study were nominally significantly higher in each pivmecillinam arm than in the placebo arm in each age group, as shown in [Table 84](#).

Table 84. Overall Response by Age Category, Micro-ITT Analysis Set, Ferry 2007 Study

Age Group Parameter	Pivmecillinam 200 mg BID x 7 Days	Pivmecillinam 200 mg TID x 7 Days	Pivmecillinam 400 mg BID X 3 Days	Placebo
Age 65+				
Success n/n (%)	16/32 (50%)	15/32 (46.9%)	11/34 (32.4%)	0/25 (0%)
Risk difference	50%	46.9%	32.4%	
95% CI for RD	29.1%, 70.9%	26%, 67.7%	13.2%, 51.5%	
p-Value	<0.001	<0.001	0.001	
Age 50-64				
Success n/n (%)	17/34 (50%)	16/22 (72.7%)	9/24 (37.5%)	2/29 (6.9%)
Risk Difference	43.1%	65.8%	30.6%	
95% CI for RD	20.7%, 65.5%	41.1%, 90.6%	5.3%, 55.9%	
p-Value	<0.001	<0.001	0.015	
Age 18-49				
Success n/n (%)	49/72 (68.1%)	54/83 (65.1%)	42/76 (55.3%)	12/80 (15%)
Risk Difference	53.1%	50.1%	40.3%	
95% CI for RD	38.4%, 67.7%	35.9%, 64.2%	25.3%, 55.2%	
p-Value	<0.001	<0.001	<0.001	

Source: Statistical Analyst and Statistics Reviewer; ([Ferry et al. 2007](#))

Abbreviations: BID, twice daily; CI, confidence interval; micro-ITT, microbiological intent-to-treat; RD, risk difference; TID, three times daily

Overall responses in the Menday study were somewhat lower in the pivmecillinam arm than in the cephalexin arm in each age group. The noninferiority of pivmecillinam to cephalexin was not demonstrated in any of the three age subgroups. See [Table 85](#) for details.

Table 85. Overall Response by Age Category, Micro-ITT Analysis Set, Menday 2000 Study

Age Group Parameter	Pivmecillinam 200 mg BID x 3 Days	Cephalexin 250 mg QID x 7 Days
Age 65+		
Success n/n (%)	10/16 (62.5%)	8/12 (66.7%)
Risk difference	-4.2%	
95% CI for RD	-47.2%, 38.8%	
p-Value	1	
Age 50-64		
Success n/n (%)	1/2 (50%)	5/7 (71.4%)
Risk difference	-21.4%	
95% CI for RD	-100%, 87.7%	
p-Value	1	
Age 18-49		
Success n/n (%)	80/109 (73.4%)	87/113 (77%)
Risk difference	-3.6%	
95% CI for RD	-15.9%, 8.7%	
p-Value	0.641	

Source: Statistical Analyst and Statistics Reviewer; ([Menday 2000](#))

Abbreviations: BID, twice daily; CI, confidence interval; micro-ITT, microbiological intent-to-treat; QID, four times daily; RD, risk difference

Overall responses in the Menday study were somewhat lower in the pivmecillinam arm than in the cephalixin arm in Caucasians, and much lower in the pivmecillinam arm than in the cephalixin arm in Black or African American subjects. The noninferiority of pivmecillinam to cephalixin was not demonstrated in any of the three race subgroups. See [Table 86](#) for details.

Table 86. Overall Response by Race, Micro-ITT Analysis Set, Menday 2000 Study

Race Parameter	Pivmecillinam 200 mg BID x 3 Days	Cephalexin 250 mg QID x 7 Days
Caucasian		
Success n/n (%)	83/112 (74.1%)	88/114 (77.2%)
Risk difference	-3.1%	
95% CI for RD	-15.2%, 9%	
p-Value	0.643	
Black or African American		
Success n/n (%)	5/11 (45.5%)	11/15 (73.3%)
Risk difference	-27.9%	
95% CI for RD	-72.7%, 17%	
p-Value	0.228	
Other Races		
Success n/n (%)	2/3 (66.7%)	1/3 (33.3%)
Risk difference	33.3%	
95% CI for RD	-75.4%, 100%	
p-Value	1	

Source: Statistical Analyst and Statistics Reviewer; ([Menday 2000](#))

Abbreviations: BID, twice daily; CI, confidence interval; micro-ITT, microbiological intent-to-treat; QID, four times daily; RD, risk difference

Overall responses in the Vik study were significantly higher in the pivmecillinam arm than in the ibuprofen arm in the 50 to 64 and 18 to 49 age groups. (There were no subjects 65 years of age and older). See [Table 87](#) for details.

Table 87. Overall Response by Age Category, Micro-ITT Analysis Set, Vik 2018 Study

Age Group Parameter	Pivmecillinam 200 mg TID x 3 Days	Ibuprofen 600 mg TID x 3 Days
Age 65+		
Success n/n (%)	0/0	0/0
Risk difference	NA	
95% CI for RD	NA	
p-Value	--	
Age 50-64		
Success n/n (%)	8/10 (80%)	1/7 (14.3%)
Risk difference	65.7%	
95% CI for RD	17.7%, 100%	
p-Value	0.015	
Age 18-49		
Success n/n (%)	61/95 (64.2%)	25/112 (22.3%)
Risk difference	41.9%	
95% CI for RD	28.6%, 55.2%	
p-Value	<0.001	

Source: Statistical Analyst and Statistics Reviewer; ([Vik et al. 2018](#))

Abbreviations: BID, twice daily; CI, confidence interval; micro-ITT, microbiological intent-to-treat; RD, risk difference; TID, three times daily

Overall responses in the Vik study were significantly higher in the pivmecillinam arm than in the ibuprofen arm in Denmark, Norway, and Sweden. See [Table 88](#) for details.

Table 88. Overall Response by Country, Micro-ITT Analysis Set, Vik 2018 Study

Country Parameter	Pivmecillinam 200 mg TID x 3 Days	Ibuprofen 600 mg TID x 3 Days
Denmark		
Success n/n (%)	7/11 (63.6%)	1/16 (6.2%)
Risk difference	57.4%	
95% CI for RD	18.9%, 95.9%	
p-Value	0.002	
Norway		
Success n/n (%)	52/81 (64.2%)	23/89 (25.8%)
Risk difference	38.4%	
95% CI for RD	23.3%, 53.4%	
p-Value	<0.001	
Sweden		
Success n/n (%)	10/13 (76.9%)	2/14 (14.3%)
Risk difference (RD)	62.6%	
95% CI for RD	25.9%, 99.4%	
p-Value	0.002	

Source: Statistical Analyst and Statistics Reviewer; ([Vik et al. 2018](#))

Abbreviations: BID, twice daily; CI, confidence interval; micro-ITT, microbiological intent-to-treat; RD, risk difference; TID, three times daily

Pivmecillinam was nominally significantly inferior to norfloxacin in subjects 50 to 64 and 18 to 49 years old. There were only two pivmecillinam subjects who were age 65 and older, so there was no statistically significant difference between the two treatment arms in older subjects, but the difference in point estimates also favored norfloxacin. See [Table 89](#) for details.

Table 89. Overall Response by Age Category, Micro-ITT Analysis Set, Nicolle 2002 Study

Age Group Parameter	Pivmecillinam 400 mg BID x 3 Days	Norfloxacin 400 mg BID x 3 Days
Age 65+ ^a		
Success n/n (%)	0/2 (0%)	4/5 (80%)
Risk difference	-80%	
95% CI for RD	-100%, -9.9%	
p-Value	0.143	
Age 50-64		
Success n/n (%)	23/47 (48.9%)	50/61 (82%)
Risk difference	-33%	
95% CI for RD	-52.2%, -13.9%	
p-Value	<0.001	
Age 18-49		
Success n/n (%)	91/156 (58.3%)	105/144 (72.9%)
Risk difference	-14.6%	
95% CI for RD	-25.9%, -3.3%	
p-Value	0.011	

Source: Statistical Analyst and Statistics Reviewer; ([Nicolle et al. 2002](#))

^a Small sample size in this age group

Abbreviations: BID, twice daily; CI, confidence interval; micro-ITT, microbiological intent-to-treat; RD, risk difference

Pivmecillinam was nominally significantly inferior to norfloxacin in subjects in Great Britain and was not shown to be noninferior to norfloxacin in Canada or France. Pivmecillinam was also nominally significantly inferior to norfloxacin in subjects in all remaining countries combined. See [Table 90](#) for details.

Table 90. Overall Response by Country, Micro-ITT Analysis Set, Nicolle 2002 Study

Country Parameter	Pivmecillinam 400 mg BID x 3 Days	Norfloxacin 400 mg BID x 3 Days
Canada		
Success n/n (%)	30/52 (57.7%)	35/49 (71.4%)
Risk difference	-13.7%	
95% CI for RD	-34.2%, 6.7%	
p-Value	0.212	
France		
Success n/n (%)	26/42 (61.9%)	37/49 (75.5%)
Risk difference	-13.6%	
95% CI for RD	-34.8%, 7.6%	
p-Value	0.179	
Great Britain		
Success n/n (%)	28/54 (51.9%)	43/54 (79.6%)
Risk difference	-27.8%	
95% CI for RD	-46.7%, -8.8%	
p-Value	0.004	
Austria, Belgium, Switzerland, Denmark, Ireland, and the Netherlands		
Success n/n (%)	30/57 (52.6%)	44/58 (75.9%)
Risk difference	-23.2%	
95% CI for RD	-42%, -4.5%	
p-Value	0.012	

Source: Statistical Analyst and Statistics Reviewer; ([Nicolle et al. 2002](#))

Abbreviations: BID, twice daily; CI, confidence interval; micro-ITT, microbiological intent-to-treat; RD, risk difference

Results from the efficacy reanalysis were similar to original efficacy trends. The Applicant noted that the percentage of microbiology responses and most of the percentages of clinical responses were consistently lower in the reanalysis compared to the original analysis, which they said reflected the more stringent criteria for declaring success in the reanalysis and inclusion of missing data as an indeterminate response. See [Table 91](#) for details.

Table 91. Comparison of Published Results and Reanalysis of Primary and Supportive Efficacy Studies

Study	Dosing Regimen	Published* / UTILITY Re-Analysis (%)	Published* / UTILITY Re-Analysis (%)
		Microbiological Response	Clinical Response
Ferry 2007	Pivmecillinam 200 mg TID, 7 days	93 / 87	62 / 64
	Pivmecillinam 200 mg BID, 7 days	94 / 87	64 / 63
	Pivmecillinam 400 BID, 3 days	84 / 75	55 / 52
	Placebo	34 / 26	25 / 23
Menday 2000	Pivmecillinam 200 mg TID, 3 days	90 / 76	95 ¹ / 83
	Cephalexin 250 mg four times/day, 7 days	82 / 80	94 ¹ / 85
Vik 2018	Pivmecillinam 200 mg TID, 3 days	90 / 74	91 ¹ / 77
	Ibuprofen 600 mg TID, 3 days	72 / 54	63 ¹ / 38
Nicolle 2002	Pivmecillinam 400 mg BID, 3 days	75 / 63	82 / 78
	Norfloxacin 400 mg BID, 3 days	91 / 79	88 / 89
Hansen 1980	Pivmecillinam 200 mg TID, 7 days	87 / 84	N/A
	Pivmecillinam 400 mg TID, 3 days	93 / ND	
Bresky 1977	Pivmecillinam 400 mg TID, 10 days	90 / ND	N/A
	Amoxicillin 375 mg TID, 10 days	82 / 48	
	Pivmecillinam 200 mg TID, 10 days	89 / 50	

Source: Table 30 in the ISE; (Bresky 1977; Hansen et al. 1981; Menday 2000; Nicolle et al. 2002; Ferry et al. 2007; Vik et al. 2018)

¹ Response rate defined as clinical cure or improvement

* Assessment of microbiological response and clinical response may differ across studies, and the definition of the populations may also differ in the reanalysis

Abbreviations: BID, twice daily; N/A, not applicable; ND, reanalysis not done for this group; TID, three times daily

The robustness of the reanalysis was also assessed using somewhat different populations which included the original microbiological intent-to-treat (micro-ITT) population used for the primary efficacy reanalysis population:

- Micro-ITT: Excluded subjects without evidence of pyuria (except for the Menday study in which pyuria data were not collected) and with less than two UTI symptoms.

Two other additional analyses were carried out by the Applicant using the following alternative populations:

- Intent-to-treat (ITT) 1: population (designated ITT-1, micro-ITT1, and expanded micro-ITT1) consisted of subjects regardless of whether pyuria was present or absent.
- ITT2: population (designated ITT2, micro-ITT2, and expanded micro-ITT2) included subjects with at least one UTI symptom.

Overall response rates were very consistent using the modified micro-ITT populations as shown in [Table 92](#).

Table 92. Overall Response Rates for Alternative Definitions, Micro-ITT Analysis Set, Primary Efficacy Studies

Study	Analysis Set ¹	Pivmecillinam 200 mg TID n/N (%) ²	Comparator ³ n/N (%) ³
Ferry 2007	Micro-ITT	85/137 (62.0)	14/134 (10.4)
	Micro-ITT1	101/166 (60.8)	17/159 (10.7)
	Micro-ITT2	88/144 (61.1)	15/146 (10.3)
Menday 2000	Micro-ITT	91/127 (71.7)	100/132 (75.8)
	Micro-ITT1	91/127 (71.7)	100/132 (75.8)
	Micro-ITT2	94/131 (71.8)	104/138 (75.4)
Vik 2018	Micro-ITT	69/105 (65.7)	26/119 (21.8)
	Micro-ITT1	71/109 (65.1)	29/130 (22.3)
	Micro-ITT2	69/105 (65.7)	26/119 (21.8)

Source: Table 32 in the ISE; (Menday 2000; Ferry et al. 2007; Vik et al. 2018)

¹ Micro-ITT excludes subjects with no evidence of pyuria (except Menday study where pyuria data was not collected) or with <2 UTI symptoms; Micro-ITT1 includes subjects regardless of evidence of pyuria and includes subjects with ≥2 UTI symptoms; and Micro-ITT2 excludes subjects with no evidence of pyuria (except Menday study where pyuria data was not collected) and includes subjects with ≥1 UTI symptom

² Represents percentages of subjects classified as an overall response success

³ Comparator = placebo (Ferry), cephalexin (Menday), or ibuprofen (Vik)

Abbreviations: ITT, intent-to-treat; micro-ITT, microbiological intent-to-treat; N, number of subjects in the micro-ITT analysis set; n, number of subjects in the specified category. Percentages are calculated as n/N x 100.; TID, three times daily; UTI, urinary tract infection

Reanalysis and Alternative Definitions

The Applicant conducted additional analyses of overall response using less stringent definitions of clinical and microbiological responses in the micro-ITT population. The three definitions of clinical and microbiological success were defined as follows:

- Reanalysis Definition: Clinical success = symptom score of 0 and microbiological success based on <10³ CFU/mL threshold
- Alternative Definition 1: Clinical success = symptom score of 0 or 1 and microbiological success based on <10⁴ CFU/mL
- Alternative Definition 2: Clinical success = symptom score of 0 or 1 and microbiological success based on <10⁵ CFU/mL

As shown in Table 93, the number of responders were observed to increase more in the pivmecillinam arm than in the placebo arm in the Ferry study leading to greater overall treatment differences. More comparable increases in both treatment arms were observed in the Menday study leading to fairly consistent overall treatment differences. (The Applicant noted that these alternative definitions were not performed for the Vik study because CFU count data were not available.)

Table 93. Overall Response Rates Based on Alternative Definitions of Clinical and Microbiological Success, Micro-ITT Analysis Set, Primary Efficacy Studies ³

Study	Outcome Definition	Pivmecillinam 200 mg TID n/N (%) ¹	Comparator ² n/N (%) ²
Ferry 2007	Re-Analysis Definition	85/137 (62.0)	14/134 (10.4)
	Alternative Definition 1	108/137 (78.8)	20/134 (14.9)
	Alternative Definition 2	108/137 (78.8)	21/134 (15.7)
Menday 2000	Re-Analysis Definition	91/127 (71.7)	100/132 (75.8)
	Alternative Definition 1	96/127 (75.6)	105/132 (79.5)
	Alternative Definition 2	99/127 (78.0)	111/132 (84.1)

Source: Table 33 in the ISE; (Menday 2000; Ferry et al. 2007)

Reanalysis Definition=clinical success defined as symptom score of 0 and microbiological success based on <10³ CFU/mL threshold.

Alternative Definition 1=clinical success defined as symptom score of 0 or 1 and microbiological success defined based on <10⁴ CFU/mL.

Alternative Definition 2= clinical success defined as symptom score of 0 or 1 and microbiological success defined based on <10⁵ CFU/mL.

¹ Represents percentages of subjects classified as an overall response success.

² Comparator = placebo (Ferry) or cephalexin (Menday).

³ Analysis not performed for Vik study because CFU counts not available

Abbreviations: CFU, colony-forming unit; micro-ITT, microbiologic intent-to-treat; N, number of subjects in the Micro-ITT analysis set; n, number of subjects in the specified category. Percentages are calculated as n/N x 100.A.; ITT, intent-to-treat; TID, three times daily

17. Clinical Safety

This section includes additional safety information and analyses performed on the three primary studies (Bresky 1977; Menday 2000; Ferry et al. 2007) and one supportive study (Nicolle et al. 2002) that were considered in the overall safety review. These supplementary analyses included analysis populations, demographic information, treatment-emergent adverse events (TEAEs) by age group, and duration of exposure.

17.1. Ferry 2007 Study

Baseline demographic information on age for the Ferry 2007 study is provided in Table 94 (Ferry et al. 2007). This was a study conducted in Sweden in female subjects with a mean age of 44 years. About 18% of subjects receiving pivmecillinam 200 mg TID for 7 days were greater than or equal to 65 years of age.

Table 94. Baseline Demographics, Safety Population, Ferry 2007 Study

Characteristic	PIVYA 200 mg TID x 7 Days N=282	PIVYA 200 mg BID x 7 Days N=294	PIVYA 400 mg BID x 3 Days N=287	Placebo N=288
Age, years				
Mean (SD)	44 (18)	43.6 (18)	43.7 (18)	41.5 (17)
Median (min, max)	41 (18, 82)	44 (18, 85)	42 (18, 88)	39 (18, 83)
Age group, years, n (%)				
≤24	62 (22)	60 (20)	61 (21)	67 (23)
25 to <50	111 (39)	120 (41)	126 (44)	127 (44)
≥50	109 (39)	114 (39)	100 (35)	94 (33)
Age group ≥65, years, n (%)				
≥65	52 (18)	47 (16)	55 (19)	41 (14)
Age group ≥75, years, n (%)				
≥75	13 (5)	10 (3)	16 (6)	14 (5)
Country of participation, n (%)				
Sweden	282 (100)	294 (100)	287 (100)	288 (100)

Source: adsl.xpt; Software: R; (Ferry et al. 2007)

Abbreviations: BID, twice daily; N, number of subjects in treatment group; n, number of subjects with given characteristic; PIVYA, pivmecillinam; SD, standard deviation; TID, three times a day

The following table provides an overview of adverse events by age groups in the safety population. No overall differences were observed between subjects 65 years of age and older compared with younger adult subjects, see [Table 95](#).

Table 95. Overview of Adverse Events by Demographic Subgroup (Age), Safety Population, Ferry 2007 Study

Characteristic	PIVYA 200 mg TID x 7 Days N=282 n/N _s (%)	PIVYA 200 mg BID x 7 Days N=294 n/N _s (%)	PIVYA 400 mg BID x 3 Days N=287 n/N _s (%)	Placebo N=288 n/N _s (%)
Age group, years				
≤24	7/62 (11)	6/60 (10)	5/61 (8)	7/67 (10)
25 to <50	18/111 (16)	15/120 (13)	17/126 (14)	12/127 (9)
≥50	22/109 (20)	12/114 (11)	15/100 (15)	13/94 (14)
Age group ≥65, years				
≥65	11/52 (21)	5/47 (11)	8/55 (15)	6/41 (15)
Age group ≥75, years				
≥75	4/13 (31)	1/10 (10)	2/16 (13)	4/14 (27)

Source: adae.xpt; Software: R; (Ferry et al. 2007)

Abbreviations: BID, twice daily; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; PIVYA, pivmecillinam; TID, three times a day

[Table 96](#) provides the duration of exposure. Note: the group receiving pivmecillinam 400 mg BID for three days also received placebo for four days. As the dataset did not flag when placebo was started, the entire duration of PIVYA plus placebo was recorded.

Table 96. Duration of Exposure, Safety Population, Ferry 2007 Study

Parameter	PIVYA 200 mg TID x 7 Days N=282	PIVYA 200 mg BID x 7 Days N=294	PIVYA 400 mg BID x 3 Days N=287	Placebo N=288
Duration of treatment, days				
Mean (SD)	8 (6)	8 (5)	8 (4)	7 (4)
Median (Q1, Q3)	7 (7, 8)	7 (7, 8)	7 (7, 8)	7 (7, 8)
Min, max	1, 46	1, 42	1, 39	1, 39
Total exposure (person years)	6	6	6	6
Subjects treated, by duration, n (%)				
<1 days	0	0	0	0
≥1 to <3 days	8 (3)	14 (5)	11 (4)	26 (9)
≥3 to <7 days	8 (3)	9 (3)	9 (3)	38 (13)
≥7 to <15 days	255 (90)	261 (89)	260 (91)	217 (75)
≥15 days	9 (3)	9 (3)	7 (2)	6 (2)
Missing	2 (1)	1 (0)	0	1 (0)

Source: adex.xpt and adsl.xpt; Software: R; (Ferry et al. 2007)

Duration is median 7 days (maximum 46 days, minimum 1 day).

Abbreviations: BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PIVYA, pivmecillinam; Q1, first quartile; Q3, third quartile; SD, standard deviation; TID, three times a day

A comprehensive list of TEAEs by preferred term is provided in [Table 97](#). For the pivmecillinam 200 mg TID group, nausea, diarrhea, vulvovaginal candidiasis, pruritis genital, and headache were the most common TEAEs, occurring in less than 1%. Pyrexia was observed more commonly in placebo recipients compared with subjects who received pivmecillinam 200 mg TID.

Table 97. Subjects With Common Adverse Events, Safety Population, Ferry 2007 Study

Preferred Term	PIVYA 200 mg TID x 7 Days N=282 n (%)	PIVYA 200 mg BID x 7 Days N=294 n (%)	PIVYA 400 mg BID x 3 Days N=287 n (%)	Placebo N=288 n (%)
Any AE	47 (16.7)	33 (11.2)	37 (12.9)	32 (11.1)
Nausea	12 (4.3)	5 (1.7)	6 (2.1)	6 (2.1)
Vulvovaginal candidiasis	5 (1.8)	3 (1)	3 (1)	0
Diarrhea	6 (2.1)	5 (1.7)	9 (3.1)	2 (0.7)
Headache	4 (1.4)	0	3 (1)	1 (0.3)
Fungal infection	2 (0.7)	0	0	0
Vaginal infection	2 (0.7)	1 (0.3)	0	0
Pruritus genital	5 (1.8)	3 (1)	3 (1)	4 (1.4)
Abdominal pain	2 (0.7)	3 (1)	2 (0.7)	1 (0.3)
Breast cancer	1 (0.4)	0	0	0
Breast pain	1 (0.4)	0	0	0
Diarrhea hemorrhagic	1 (0.4)	0	0	0
Dry mouth	1 (0.4)	0	1 (0.3)	0
Dry skin	1 (0.4)	0	0	0
Gastritis	1 (0.4)	2 (0.7)	1 (0.3)	0
Hematuria	1 (0.4)	0	0	0
Periorbital oedema	1 (0.4)	0	0	0
Chills	1 (0.4)	0	0	1 (0.3)
Menstrual disorder	1 (0.4)	0	0	1 (0.3)
Pruritus	1 (0.4)	1 (0.3)	1 (0.3)	1 (0.3)
Vertigo	1 (0.4)	1 (0.3)	0	1 (0.3)
Back pain	0	0	1 (0.3)	0

	PIVYA 200 mg TID x 7 Days N=282	PIVYA 200 mg BID x 7 Days N=294	PIVYA 400 mg BID x 3 Days N=287	Placebo N=288
Preferred Term	n (%)	n (%)	n (%)	n (%)
Cough	0	0	1 (0.3)	0
Discharge	0	0	1 (0.3)	0
Dyspepsia	0	1 (0.3)	0	0
Dysphonia	0	0	1 (0.3)	0
Dystonia	0	1 (0.3)	0	0
Erysipelas	0	1 (0.3)	0	0
Flank pain	0	0	1 (0.3)	0
Gastroenteritis	0	3 (1)	0	0
Hypoesthesia	0	0	1 (0.3)	0
Infectious mononucleosis	0	1 (0.3)	0	0
Micturition disorder	0	0	1 (0.3)	0
Myalgia	0	0	1 (0.3)	0
Oral mucosal eruption	0	1 (0.3)	0	0
Rhinitis	0	1 (0.3)	0	0
Tendonitis	0	0	1 (0)	0
Throat tightness	0	0	1 (0)	0
Fatigue	2 (1)	3 (1)	2 (1)	3 (1)
Constipation	1 (0)	1 (0)	0	2 (1)
Vomiting	1 (0)	1 (0)	1 (0)	2 (1)
Eczema	0	0	0	1 (0)
Gastric dilatation	0	0	0	1 (0)
Musculoskeletal chest pain	0	0	0	1 (0)
Musculoskeletal pain	0	0	1 (0)	1 (0)
Pain in extremity	0	0	0	1 (0)
Rash	0	0	0	1 (0)
Upper respiratory tract infection	0	1 (0)	0	1 (0)
Vaginal ulceration	0	0	0	1 (0)
Decreased appetite	0	1 (0)	0	2 (1)
Pyrexia	0	0	2 (0.7)	5 (2)

Source: adae.xpt; Software: R; (Ferry et al. 2007)

Asterisk (*) indicates that 95% confidence interval excludes zero.

Treatment-emergent adverse events defined as an adverse event occurring up through Day 30.

Duration is median 7 days (maximum 46 days, minimum 1 day).

Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; BID, twice daily; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PIVYA, pivmecillinam; TID, three times a day

17.2. Menday 2000 Study

Menday 2000 was the only study for which data on race and ethnicity was collected although both race and ethnicity were combined (Menday 2000). Overall demographics by age group and race/ethnicity are provided in Table 98. In the pivmecillinam group, subjects ≥65 years of age comprised 9% of the safety population. All subjects in this study were enrolled in the U.S. Most subjects in the pivmecillinam group were Caucasian (85%), followed by Black (11%), Asian (2%), and Hispanic (1%).

Table 98. Baseline Demographic and Clinical Characteristics, Safety Population, Menday 2000 Study

Characteristic	PIVYA 200 mg TID x 3 Days N=213	Cephalexin 250 mg QID x 7 Days N=219
Age, years		
Mean (SD)	31 (16)	31 (16)
Median (min, max)	24 (18, 85)	24 (18, 87)
Age group, years, n (%)		
≤24	109 (51)	113 (52)
25 to <50	80 (38)	78 (36)
≥50	24 (11)	28 (13)
Age group ≥65, years, n (%)		
≥65	19 (9)	17 (8)
Age group ≥75, years, n (%)		
≥75	5 (2)	8 (4)
Race, n (%)		
Caucasian	180 (85)	186 (84)
Black	24 (11)	28 (13)
Asian	4 (2)	3 (1)
Hispanic	3 (1)	2 (1)
Other	1 (1)	0
Missing	1 (1)	0
Country of participation, n (%)		
United States	213 (100)	219 (100)

Source: adsl.xpt and Menday.xpt; Software: R; ([Menday 2000](#))

Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; PIVYA, pivmecillinam; QID, four times daily; SD, standard deviation; TID, three times a day

17.3. Bresky 1977 Study

Demographic information on age provided in [Table 99](#). In the group receiving pivmecillinam 200 mg TID, 11% were 65 years of age or older.

Table 99. Baseline Demographic (Age), Safety Population, Bresky 1977 Study

Characteristic	PIVYA 200 mg TID x 10 Days N=84	PIVYA 400 mg TID x 10 Days N=114	Amoxicillin 375 mg TID x 10 Days N=142
Age, years			
Mean (SD)	42 (16)	39.7 (18)	37 (16)
Median (min, max)	43 (18, 75)	36 (18, 75)	32 (18, 74)
Age group, years, n (%)			
≤24	16 (19)	33 (29)	43 (30)
25 to <50	39 (46)	41 (36)	63 (44)
≥50	29 (35)	40 (35)	36 (25)
Age group ≥65, years, n (%)			
≥65	9 (11)	11 (10)	14 (10)
Age group ≥75, years, n (%)			
≥75	1 (1)	1 (1)	0
Country of participation, n (%)			
Sweden	84 (100)	114 (100)	142 (100)

Source: adsl.xpt; Software: R; ([Menday 2000](#))

Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; PIVYA, pivmecillinam; SD, standard deviation; TID, three times daily

17.4. Nicolle 2002 Study

Baseline demographic information by age group and country of participation is presented in [Table 100](#).

Table 100. Baseline Demographics, Safety Population, Nicolle 2002 Study

Characteristic	PIVYA 400 mg BID x 3 Days N=479	Norfloxacin 400 mg BID x 3 Days N=467
Age, years		
Mean (SD)	39 (13)	38 (13)
Median (min, max)	38 (18, 84)	36 (18, 79)
Age group, years, n (%)		
≤24	79 (17)	82 (18)
25 to <50	295 (62)	278 (60)
≥50	105 (22)	107 (23)
Age group ≥65, years, n (%)		
≥65	4 (1)	8 (2)
Age group ≥75, years, n (%)		
≥75	1 (0)	1 (0)
Country of participation, n (%)		
Canada	108 (23)	110 (24)
France	105 (22)	93 (2)
Great Britain	140 (29)	145 (31)
Others	126 (26)	119 (25)

Source: adsl.xpt; Software: R; ([Nicolle et al. 2002](#))

Abbreviations: BID, twice daily; N, number of subjects in treatment group; n, number of subjects with given characteristic; PIVYA, pivmecillinam; SD, standard deviation

[Table 101](#) provides the duration of exposure. While the median duration of therapy was three days, three subjects in the pivmecillinam group receive six or more days of therapy.

Table 101. Duration of Exposure, Safety Population, Nicolle 2002 Study

Parameter	PIVYA 400 mg BID x 3 Days N=479	Norfloxacin 400 mg BID x 3 Days N=467
Duration of treatment, days		
Mean (SD)	3.5 (2)	3.4 (1)
Median (Q1, Q3)	3 (3, 4)	3 (3, 4)
Min, max	1, 34	1, 6
Total exposure (person years)	5	4
Subjects treated, by duration, n (%)		
<1 days	0	0
≥1 to <3 days	5 (1)	10 (2)
≥3 to <6 days	460 (96)	450 (96)
≥6 to <12 days	2 (0)	1 (0)
≥12 days	1 (0)	0
Missing	11 (2)	6 (1)

Source: adsl.xpt; Software: R; ([Nicolle et al. 2002](#))

Duration is median 3 days (maximum 34 days, minimum 1 day).

Abbreviations: BID, twice daily; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PIVYA, pivmecillinam; Q1, first quartile; Q3, third quartile; SD, standard deviation

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

19.1. Nonclinical Microbiology

In Vitro MIC Data and Spectrum of Activity: US Surveillance Studies (2018-2020)

In vitro MIC data of MEC and other comparator drugs were submitted against 3,303 recent Enterobacterales UTI isolates from the US surveillance studies between 2018 to 2020 ([Table 102](#)) [IHMA combined report (3500, 4118, 4504)]. MIC tests were performed by agar dilution method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. Against Enterobacterales isolates, the MIC₅₀/MIC₉₀ of MEC was 0.25/4 µg/mL with an MIC range of ≤0.015 to >128 µg/mL. Using the CLSI susceptible MIC cut-off of ≤8 µg/mL for MEC ([CLSI 2024](#)), 94.5% to 95.3% isolates appeared to be susceptible.

Table 102. In Vitro MIC Data of Mecillinam and Comparators Against Enterobacterales Isolates (N=3,303) From the U.S. Surveillance Studies (2018-2020)

Drug		MIC (µg/mL)				CLSI Susceptibility		
		MIC ₅₀	MIC ₉₀	MIN	MAX	%S	%I	%R
2018	Ceftriaxone	0.03	>8	≤0.015	>8	79.9	0.5	19.6
	Ciprofloxacin	0.015	>8	≤0.002	>8	71.5	2.5	26.0
	Fosfomycin	2	32	≤0.06	>256	95.7	2.3	2.0
	Mecillinam	0.25	4	0.03	>128	94.5	1.5	4.0
	Nitrofurantoin	16	64	≤2	>128	70.6	19.8	9.5
	TMP-SMX	0.12	>8	≤0.015	>8	70.5	-	29.5
2019	Ceftriaxone	0.03	>8	≤0.015	>8	81.4	0.6	18.0
	Ciprofloxacin	0.015	>8	≤0.002	>8	77.4	2.0	20.6
	Fosfomycin	1	32	0.25	>256	97.6	0.7	1.7
	Mecillinam	0.25	4	0.03	>128	95.0	1.0	4.0
	Nitrofurantoin	16	128	≤2	>128	69.6	14.4	16.0
	TMP-SMX	0.12	>8	≤0.015	>8	73.8	-	26.2
2020	Ceftriaxone	0.06	>8	≤0.015	>8	79.2	0.8	20.0
	Ciprofloxacin	0.015	>8	0.004	>8	80.2	1.8	18.1
	Fosfomycin	2	32	0.25	>256	97.9	1.1	1.0
	Mecillinam	0.25	4	≤0.015	>128	95.3	1.5	3.3
	Nitrofurantoin	16	128	≤2	>128	70.5	18.6	10.9
	TMP-SMX	0.12	>8	≤0.015	>8	74.0	-	26.0

Source: NDA submission/ 2.7.2 Summary of Clinical Pharmacology/ Table 29
Abbreviations: CLSI, Clinical and Laboratory Standards Institute; MAX, maximum; MIC, minimum inhibitory concentration; MIN, minimum; TMP-SMX, trimethoprim/sulfamethoxazole

The antibacterial spectrum of activity of MEC includes susceptible gram-negative isolates of Enterobacterales species that are associated with UTIs, e.g., *Citrobacter freundii*, *Enterobacter cloacae*, *E. coli*, *K. aerogenes*, *K. oxytoca*, *K. pneumoniae*, and *P. mirabilis*.

Against 154 *C. freundii*, 301 *E. cloacae*, 1869 *E. coli* (including 224 ESBL-positive and 1645 ESBL-negative), 154 *K. aerogenes*, 170 *K. oxytoca*, 348 *K. pneumoniae* (including 155 ESBL-positive and 193 ESBL-negative), and 307 *P. mirabilis*, the MIC₅₀/MIC₉₀ values were 0.25/1 µg/mL, 0.25/2 µg/mL, 0.25/2 µg/mL, 0.25/2 µg/mL, 0.25/8 µg/mL, 0.5/64 µg/mL, and 0.5/16 µg/mL, respectively. ESBL was determined using the CLSI-recommended broth MIC determination among *E. coli* and *K. pneumoniae* isolates only. Isolates were deemed ESBL-positive if the presence of clavulanic acid reduced ceftazidime and/or cefotaxime MIC by 3 or more doubling dilutions. MEC susceptibility rates were 98.2% and 80% against ESBL-positive 224 *E. coli* and 155 *K. pneumoniae* surveillance isolates respectively.

[Table 103](#) summarizes the antibacterial activity and susceptibility to MEC (based on the CLSI susceptible cut-off of ≤8 µg/mL) by bacterial species.

Table 103. In Vitro Activity and Susceptibility to Mecillinam Against Enterobacterales Isolates From the U.S. Surveillance Studies (2018-2020)

Organism	n	%S	%I	%R	MIC ₅₀	MIC ₉₀	MIC _{MIN}	MIC _{MAX}
<i>Citrobacter freundii</i>	154	98.1	0.7	1.3	0.25	1	≤0.015	> 128
<i>Enterobacter cloacae</i>	301	97.7	0.3	2.0	0.25	2	0.06	> 128
<i>E. coli</i>	1,869	97.5	1.0	1.4	0.25	2	≤0.015	> 128
<i>E. coli</i> ESBL-positive	224	98.2	0.5	1.3	0.5	2	0.06	> 128
<i>E. coli</i> ESBL-negative	1,645	97.5	1.1	1.5	0.25	2	≤0.015	> 128
<i>K. aerogenes</i>	154	93.5	0.0	6.5	0.25	2	0.06	> 128
<i>K. oxytoca</i>	170	90.0	0.6	9.4	0.25	8	0.06	> 128
<i>K. pneumoniae</i>	348	87.1	1.2	11.8	0.5	64	0.06	> 128
<i>K. pneumoniae</i> ESBL-positive	155	80.0	1.3	18.7	1	> 128	0.25	> 128
<i>K. pneumoniae</i> ESBL-negative	193	92.8	1.0	6.2	0.25	1	0.06	> 128
<i>Proteus mirabilis</i>	307	87.3	5.5	7.1	0.5	16	0.06	> 128

Source: IHMA combined report (3500, 4118, 4504)

Note: %S / %I / %R, percentage of isolates susceptible, intermediate, or resistant.

Note: MIC₅₀, MIC₉₀, MIC_{MIN} and MIC_{MAX} are given in µg/mL.

Abbreviations: ESBL, extended spectrum beta-lactamase; I, intermediate; MIC, minimum inhibitory concentration; MIN, minimum; R, resistant; S, susceptible

In Vitro Activity Against ESBL-Producing Enterobacterales

In vitro activities of MEC and other comparators against genetically characterized ESBL- and carbapenemase-producing Enterobacterales clinical isolates have been reported in various studies. Susceptibility and resistance were evaluated using the CLSI or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) published interpretive criteria. Overall, MEC was reported to be active against CTX-M- (variants included 1, 14, 15, 27), AmpC-, TEM-1-, OXA-1-, NDM-1-, OXA-48-like-, IMI-, IMP-producing *E. coli* and some *K. pneumoniae* isolates. Most *E. coli* isolates were susceptible to MEC compared to *K. pneumoniae*. These data correlated well with the in vitro activity of MEC against phenotypic ESBL-positive isolates of *E. coli* and *K. pneumoniae* from 2018-2020 US surveillance study ([Table 103](#)).

Interaction With Other Antimicrobials ([Fatsis-Kavalopoulos et al. 2020](#))

MEC has been studied in combination with other antimicrobials that are used to treat UTIs including nitrofurantoin (NIT), trimethoprim (TMP), MEC, ciprofloxacin (CIP), and fosfomycin

(FOF). Against 12 different *E. coli* UTI isolates tested, most of the combinations were shown to be additive in nature, with NIT-CIP, MEC-CIP, TMP-CIP, MEC-FOF, TMP-FOF being additive against all tested isolates. FOF-CIP exhibited a statistically significant antagonistic interaction for one isolate but was observed to have an additive behavior for all remaining isolates. In contrast, NIT-FOF had a significant positive interaction for one isolate but was additive for all other isolates. Synergy for TMP-NIT was detected for only 4 out of 12 UTI isolates. TMP-MEC exhibited synergy for 3 out of the 12 isolates. The MEC-NIT combination exhibited strong antagonistic behavior that was detected in all isolates tested.

Cross-resistance Between MEC and Other Agents

No cross-resistance has been reported between MEC and other β -lactam classes of antibacterial drugs. The mechanism of action of MEC is inhibition of PBP-2 that complements other β -lactams that also target peptidoglycan synthesis for cell-wall inhibition by binding to PBP-3, and PBP-1.

Antimicrobial Susceptibility Testing (AST) Methods: CLSI methods

AST of MEC in liquid medium is not recommended to determine the MIC due to issues related to reproducibility and trailing endpoints. Therefore, agar dilution MIC is the standard method for AST. Quality control (QC) ranges and breakpoints were previously established and published by CLSI for both disk testing and agar dilution assays for *E. coli* (Skov et al. 2005). CLSI Tier 2 multicenter QC studies were conducted in accordance with CLSI protocols to establish agar dilution MIC and disk diffusion QC parameters using an *E. coli* ATCC 25922 strain. These in vitro studies were performed in 8 microbiology laboratories that included testing of 10 replicates of the QC strain using 3 lots of Mueller-Hinton agar (MHA) media from 3 different manufacturers (Lots #9909-128, #125603^{(b) (4)}, #220164), and 2 lots of mecillinam 10 mcg disks from two different manufacturers (^{(b) (4)}, Lot#224533, and ^{(b) (4)}, Lot#0040742). Ampicillin 10 mcg disks (^{(b) (4)}, Lot#9302721) were used as control. QC ranges for the MIC and disk diffusion zone diameters for QC strain tested are presented in [Table 104](#).

Table 104. CLSI-Approved QC Ranges for Mecillinam Using CLSI MIC and Disk Diffusion Methods

Organism	MIC Range [μ g/mL]	Disk Diffusion Range [mm]
<i>E. coli</i> ATCC 25922	0.03–0.25	24–30

Source: CLSI and EUCAST QC range

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration; QC, quality control

In response to the FDA IR, the Applicant provided information from CLSI (June 2000) used to support the inclusion of mecillinam into CLSI tables. The submission included the establishment of QC parameters for *E. coli* ATCC25922 strain based on Tier 2 study performed in 8 microbiology laboratories.

Susceptibility Testing Interpretive Criteria (STIC)/Breakpoints for MEC

The Applicant referenced the agar dilution MIC and disk diffusion breakpoints for MEC that were published by CLSI in the USA and by EUCAST in Europe. However, the Applicant did not propose or provide any rationale for MEC STICs. Instead, the following statements (copied verbatim) were provided:

“Both CLSI and EUCAST have established clinical breakpoints for MEC when used to treat uUTI (Table 105). Based on the PTA simulations, a breakpoint of 32 mg/L is suggested for Enterobacterales and *S. saprophyticus*.”

Table 105 summarizes the MEC breakpoints for different uUTI pathogens published by CLSI and EUCAST.

Table 105. CLSI and EUCAST Breakpoints for Mecillinam

SDO	Pathogens	MIC (µg/mL)			Disk Content µg	Disk Diffusion Zone Diameter (mm)		
		S (≤)	I (=)	R (≥)		S (≥)	I (=)	R (≤)
CLSI	<i>E. coli</i> (UTI only)	8	16	32	10	15	12-14	11
EUCAST	Enterobacterales (uUTI only) (<i>E. coli</i> , <i>Citrobacter</i> spp., <i>Klebsiella</i> spp., <i>Raoultella</i> spp., <i>Enterobacter</i> spp., and <i>P. mirabilis</i>)	<8	NA	>8	10	>15	NA	<15

Source: Clinical Microbiology Reviewer created table using CLSI and EUCAST published mecillinam breakpoints
Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; I, intermediate; MIC, minimum inhibitory concentration; NA, not applicable; R, resistant; S, susceptible; SDO, Standard Developing Organization; UTI, urinary tract infections; uUTI, uncomplicated urinary tract infections

The Agency relied on the in vitro data generated from the Tier 2 QC studies and the MEC breakpoints proposal that were submitted to the Subcommittee on Antimicrobial Susceptibility Testing of NCCLS for Insertion of Mecillinam onto the M100 Supplemental Tables of the M2 Standard.

The regression lines that represent the agreement for disk diffusion (DD) zone diameters to agar dilution MICs were generated for 3 groups of Enterobacterales isolates: all Enterobacterales (n =536), UTI isolates comprising *E. coli*, *Klebsiella*, *Citrobacter*, *Enterobacter*, *Proteus* (n= 489), and UTI pathogen *E. coli* only (n= 178). The correlation coefficients for the regression lines (r) were for all Enterobacterales 0.82 (82%); UTI pathogens (*E. coli*, *Klebsiella*, *Citrobacter*, *Enterobacter*, *Proteus*) 0.83 (83%); and *E. coli* only 0.91 (91%). Against all isolates, the regression line was 0.85 (85%). Error-bounded rates were calculated and found acceptable based on the CLSI M23 guidelines.

In Vivo Activity: Animal Models of Infection

In vivo activities of MEC were demonstrated in mouse models of neutropenic thigh infection, UTI, and meningitis. MEC in vivo efficacy was demonstrated against infections caused by *E. coli* in these models. This review will focus only the neutropenic thigh and UTI infection models.

Mouse Neutropenic Thigh Infection (Jacqueline, 2022)

The in vivo activities and PK/PD parameters of MEC were studied in mouse neutropenic thigh infection model against four clinical isolates of *E. coli* with different MEC MICs (0.38 to 16 mg/L).

Briefly, six-week-old, specific pathogen-free, female RjOrl:SWISS mice were used for these studies. Treatment and control groups were composed of three mice each. Mice were rendered transiently neutropenic prior to the infection. Thigh infection for each isolate was induced by

injecting 100 µL of the inoculum into each thigh of mice 2 hours prior to the start of therapy with MEC. Animals were treated with MEC at 200 mg/kg by subcutaneous injections for 24 hours. Control animals received phosphate buffer saline and were euthanized just prior to therapy initiation and after 24 hours. Twenty-four hours after infection, mice were euthanized, thighs were homogenized, and plated for enumeration of viable bacteria.

The PK/PD studies confirmed that %T>MIC was the PK parameter that most closely correlated with in vivo efficacy for *E. coli*. For MEC the %T>MIC required for microbiologic stasis with *E. coli* was between 20.7% and 50.7% of the dosing interval. The mean %T>MIC value for efficacy against all *E. coli* strains was 30.1% of the dosing interval. [Table 106](#) summarizes the in vitro, in vivo, and PD results of MEC against the tested organisms.

Table 106. Mecillinam PD Parameters Against *E. coli* in a Neutropenic Mouse Thigh Model

Strain	Resistance Determinant	MIC [mg/L]	R ²	% T>MIC	
				Stasis	1-log CFU Killing
ATL#EC20	OXA-48	0.38	0.77	22.43	73.30
ATL#EC46	ESBL	1.5	0.93	26.66	88.9
ATL#EC29	NDM-1	4	0.88	20.72	Not achieved
IHMA#2082239	ESBL	16	0.79	50.73	Not achieved

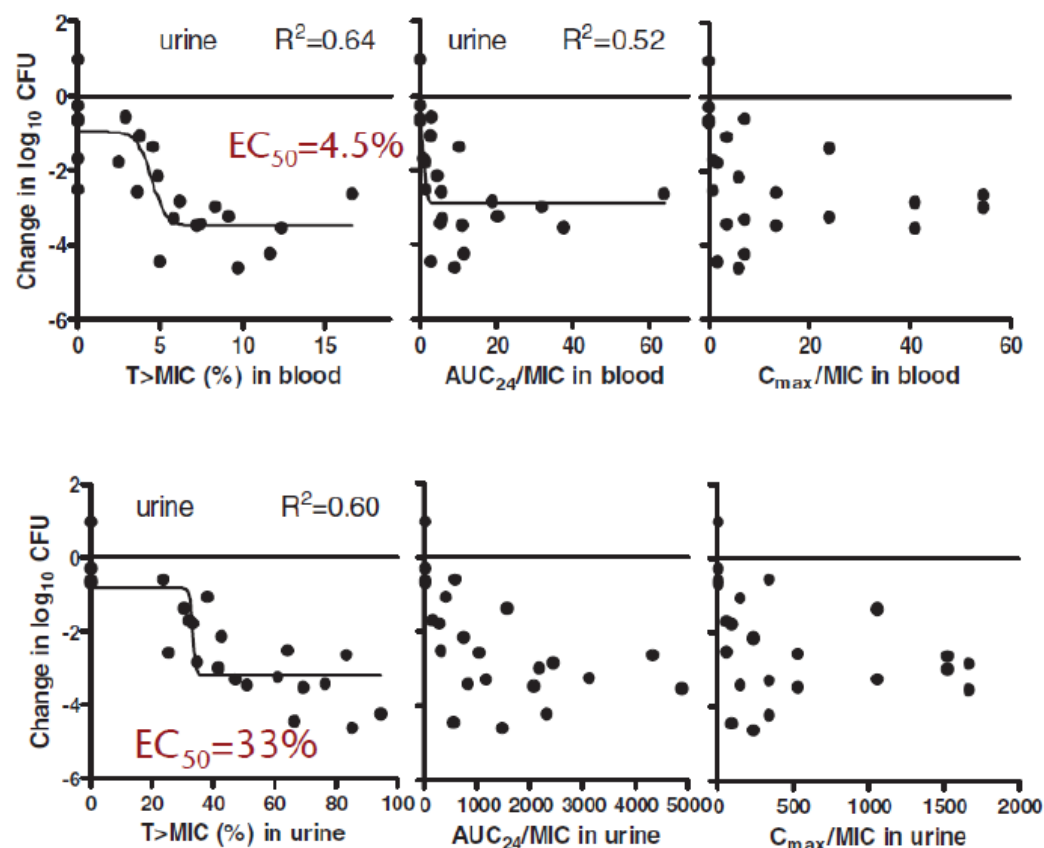
Source: Jacqueline 2022

Abbreviations: CFU, colony-forming unit; MIC, minimum inhibitory concentration; PD, pharmacodynamic

Mouse Urinary Tract Infections ([Vingsbo Lundberg C et al. 2009](#))

A UTI model in OF-1 mice was used to study the MEC in vivo efficacy and to identify the PK/PD index that best correlates with the efficacy. Briefly, urinary tract infection in mice was induced via urethral catheterization, with an ESBL-producing (CTX-M9) *E. coli*. Mice (n=8) were treated once, twice, or four times daily at Day 1 and Day 2 post infection. Urine, bladders, and kidneys were collected at Day 3 postinfection for CFU determination. PK parameters were dose dependent; and %T>MIC ranged from 0 to 120 minutes in blood, and 4 to 10 hours in urine. The maximum AUC₀₋₂₄ in blood was 15.9 h·mg/L and in urine 1,084 h·mg/L. Significant (p<0.05) CFU reduction was observed after single daily dosing with >33.3 mg/kg, only, in urine, after 2 daily doses >4.2 mg/kg both in urine and in bladders, and after 4 daily doses of >2.1 mg/kg an effect was seen in urine, bladders, and kidneys. The relationship between bacterial reduction and the PD parameters showed that %T>MIC best correlated with in vivo efficacy. The %T>MIC in blood resulting in half maximal effective concentration in urine was 4.5%, in bladder 4.9%, and in kidney 2.9%, and the coefficient of determination R² was 0.64, 0.63, and 0.66, respectively. The %T>MIC in urine resulting in half maximal effective concentration in urine was 33%, and in the bladder 46% with R² of 0.60 and 0.68, respectively ([Figure 10](#)).

Figure 10. PK/PD Indices in Blood and Urine for Efficacy in Urine



Source: ([Vingsbo Lundberg C et al. 2009](#))

Abbreviations: AUC, area under the concentration-time curve; CFU, colony-forming unit; C_{max} , maximum plasma concentration; EC_{50} , half maximal effective concentration; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; R, resistance

19.2. Microbiology Data From Primary Clinical Efficacy Studies

The efficacy of MEC compared to placebo or other comparators in adult subjects with uUTI caused by Enterobacterales and *S. saprophyticus* isolates was evaluated in three studies: Ferry, Menday, and Vik ([Menday 2000](#); [Ferry et al. 2007](#); [Vik et al. 2018](#)).

Primary Efficacy Studies (Ferry, 2007; Menday, 2000; and Vik, 2018)

Analysis Populations

The efficacy populations were defined as follows:

- ITT: All randomized subjects regardless of whether or not the subject received study drug:
- Micro-ITT: All subjects in the ITT population with a positive baseline urine culture ($\geq 10^5$ CFU/mL of a uropathogen where CFU count was available); no more than two species of microorganisms regardless of colony count; and no baseline pathogen nonsusceptible to active comparator study drug. Analyses are presented by the treatment group to which the subject was randomized.
- Expanded Micro-ITT: All subjects in the ITT population with a positive baseline urine culture ($\geq 10^5$ CFU/mL of a uropathogen), regardless of susceptibility, and no more than two species of microorganisms regardless of colony count.

Primary Efficacy Endpoint: Overall Response

The primary efficacy endpoint was the overall response at the TOC visit for each subject in the micro-ITT population that included microbiological response (both at the subject-level and by pathogen), and clinical response. TOC visits were defined as Days 8 to 10 for Ferry, Day 10 $\pm$ 2 days for Menday, and Day 14 for Vik-Study.

Baseline Pathogens in Primary Efficacy Studies (Micro-ITT Population)

Among 754 total subjects in the micro-ITT analysis population from all three efficacy studies, *E. coli* was the most prevalent uropathogen at baseline, being isolated from 623/754 (82.6%) subjects. The next most prevalent uropathogen was *S. saprophyticus* (48/754; 6.4%), followed by *P. mirabilis* (24/754; 3.2%), *Klebsiella spp.* (17/754; 2.3%), *Enterobacter spp.* (14/754; 1.9%), and *K. pneumoniae* (10/754; 1.3%). Less frequent pathogens included *Enterococcus spp.* (10/754; 1.3%), *Citrobacter spp.* (4/754; 0.5%), *S. aureus* (4/754; 0.5%), *C. koseri* (2/754; 0.3%) and *E. faecalis* (2/754; 0.3%). Monomicrobial gram-negative infections were present in most subjects (689/754; $\geq 91.4\%$). [Table 107](#) summarizes the baseline pathogens from all three primary efficacy studies.

Table 107. Baseline Pathogens, Micro-ITT Analysis Set, Primary Efficacy Studies

	Ferry (2007)		Menday (2000)		Vik (2018)	
	Pivmecillinam 200 mg TID x 7 days (N=137) n (%)	Placebo (N=134) n (%)	Pivmecillinam 200 mg TID x 3 days (N=127) n (%)	Cephalexin 250 mg QID x 7 days (N=132) n (%)	Pivmecillinam 200 mg TID x 3 days (N=105) n (%)	Ibuprofen 600 mg TID x 3 days (N=119) n (%)
Gram-Negative						
Enterobacteriaceae						
Citrobacter koseri	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)
Citrobacter species	1 (0.7)	2 (1.5)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Enterobacter species	2 (1.5)	5 (3.7)	1 (0.8)	1 (0.8)	3 (2.9)	2 (1.7)
Escherichia coli	121 (88.3)	107 (79.9)	104 (81.9)	107 (81.1)	88 (83.8)	96 (80.7)
Klebsiella pneumoniae	0 (0.0)	0 (0.0)	4 (3.1)	3 (2.3)	2 (1.9)	1 (0.8)
Klebsiella species	6 (4.4)	8 (6.0)	2 (1.6)	1 (0.8)	0 (0.0)	0 (0.0)
Proteus mirabilis	1 (0.7)	0 (0.0)	9 (7.1)	13 (9.8)	0 (0.0)	1 (0.8)
Gram-Positive						
Enterococcus faecalis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)
Enterococcus species	4 (2.9)	6 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Staphylococcus aureus	2 (1.5)	1 (0.7)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Staphylococcus saprophyticus	2 (1.5)	6 (4.5)	7 (5.5)	6 (4.5)	12 (11.4)	15 (12.6)
Monomicrobial Gram-negative infection	129 (94.2)	121 (90.3)	119 (93.7)	125 (94.7)	93 (88.6)	102 (85.7)
Monomicrobial Gram-positive infection	6 (4.4)	12 (9.0)	7 (5.5)	7 (5.3)	12 (11.4)	17 (14.3)
Polymicrobial infection	2 (1.5)	1 (0.7)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISE Table 1.5.1.1; (Menday 2000; Ferry et al. 2007; Vik et al. 2018)

Percentages are calculated as n/N x 100.

Abbreviations: ITT, intent-to-treat; micro-ITT, microbiological intent-to-treat; N, number of subjects in the micro-ITT analysis set; n, number of subjects in the specific category; QID, four times daily; TID, three times daily

Overall Response (Microbiological and Clinical Response) at TOC by Baseline Pathogens (Micro-ITT Population)

Table 108 summarizes the overall response rates at TOC for the baseline pathogens from the micro-ITT population of all primary efficacy studies. Overall success rates were high in MEC treatment arms, ranging from 63.6% to 74% against the major pathogen, *E. coli*. Against *P. mirabilis*, and *S. saprophyticus*, the success rates in MEC arm ranged from 66.7% to 100% and 50% to 58.3%, respectively.

Table 108. Overall Success at Test-of-Cure by Baseline Pathogen, Micro-ITT Analysis Set, Primary Efficacy Studies

	Ferry (2007)		Menday (2000)		Vik (2018)	
	Pivmecillinam 200 mg TID x 7 days (N=137) n/N1 (%)	Placebo (N=134) n/N1 (%)	Pivmecillinam 200 mg TID x 3 days (N=127) n/N1 (%)	Cephalexin 250 mg QID x 7 days (N=132) n/N1 (%)	Pivmecillinam 200 mg TID x 3 days (N=105) n/N1 (%)	Ibuprofen 600 mg TID x 3 days (N=119) n/N1 (%)
Gram-Negative						
Enterobacteriaceae						
Citrobacter koseri	N/A	N/A	N/A	N/A	N/A	0/2 (0.0)
Citrobacter species	1/1 (100.0)	0/2 (0.0)	1/1 (100.0)	N/A	N/A	N/A
Enterobacter species	1/2 (50.0)	1/5 (20.0)	1/1 (100.0)	1/1 (100.0)	1/3 (33.3)	1/2 (50.0)
Escherichia coli	77/121 (63.6)	10/107 (9.3)	77/104 (74.0)	82/107 (76.6)	60/88 (68.2)	21/96 (21.9)
Klebsiella pneumoniae	N/A	N/A	1/4 (25.0)	2/3 (66.7)	1/2 (50.0)	0/1 (0.0)
Klebsiella species	3/6 (50.0)	1/8 (12.5)	1/2 (50.0)	0/1 (0.0)	N/A	N/A
Proteus mirabilis	1/1 (100.0)	N/A	6/9 (66.7)	8/13 (61.5)	N/A	0/1 (0.0)
Gram-Positive						
Enterococcus faecalis	N/A	N/A	N/A	N/A	N/A	0/2 (0.0)
Enterococcus species	1/4 (25.0)	2/6 (33.3)	N/A	N/A	N/A	N/A
Staphylococcus aureus	1/2 (50.0)	0/1 (0.0)	N/A	1/1 (100.0)	N/A	N/A
Staphylococcus saprophyticus	1/2 (50.0)	0/6 (0.0)	4/7 (57.1)	6/6 (100.0)	7/12 (58.3)	4/15 (26.7)

Source: ISE Table 2.5.1.1; ([Menday 2000](#); [Ferry et al. 2007](#); [Vik et al. 2018](#))

Percentages are calculated as n/N x 100.

Abbreviations: ITT, intent-to-treat; micro-ITT, microbiological intent-to-treat; N, number of subjects in the micro-ITT analysis set; n, number of subjects with overall success at TOC visit; N/A, not applicable; N1, number of subjects with specified baseline pathogen; QID, four times daily; TID, three times daily; TOC, test-of-cure

In Vitro Activity of MEC Against Baseline Isolates from Primary Efficacy Studies

No in vitro MIC data of MEC against baseline isolates were provided from any of the efficacy studies in the NDA submission. AST of MEC for baseline isolates were conducted by DD analysis. The MIC interpretations of baseline and follow-up isolates in the microbiology datasets were made using the CLSI DD criteria that corresponded to CLSI MIC criteria i.e., susceptible (S) ≤ 8 $\mu\text{g/mL}$, intermediate-susceptible (I) 16 $\mu\text{g/mL}$, and resistant (R) ≥ 32 $\mu\text{g/mL}$ published by the CLSI for MEC breakpoints ([Table 105](#)).

AST results of baseline isolates that achieved overall success categorized as susceptible, intermediate, and resistant are provided in the following [Table 109](#).

Table 109. Mecillinam Antimicrobial Susceptibility Testing Interpretation of Baseline Isolates Achieved Overall Success at TOC, Micro-ITT Analysis Set

Table 2.8.1.1 - Group 1.1E

Overall Success at Test of Cure by Baseline Pathogens and Susceptibility to Study Drug Received
Micro-ITT Analysis Set

	Ferry (2007)		Menday (2000)		Vik (2018)	
	Pivmecillinam 200 mg tid x 7 days (N=137) n/N1 (%)	Placebo (N=134) n/N1 (%)	Pivmecillinam 200 mg tid x 3 days (N=127) n/N1 (%)	Cephalexin 250 mg qid x 7 days (N=132) n/N1 (%)	Pivmecillinam 200 mg tid x 3 days (N=105) n/N1 (%)	Ibuprofen 600 mg tid x 3 days (N=119) n/N1 (%)
Gram-Negative						
Enterobacteriaceae						
Citrobacter koseri						
Resistant	N/A	N/A	N/A	N/A	N/A	0/2 (0.0)
Citrobacter species						
Susceptible	1/1 (100.0)	N/A	1/1 (100.0)	N/A	N/A	N/A
Resistant	N/A	0/2 (0.0)	N/A	N/A	N/A	N/A
Enterobacter species						
Susceptible	1/2 (50.0)	N/A	1/1 (100.0)	1/1 (100.0)	N/A	N/A
Resistant	N/A	1/5 (20.0)	N/A	N/A	1/3 (33.3)	1/2 (50.0)
Escherichia coli						
Susceptible	66/109 (60.6)	N/A	72/97 (74.2)	80/103 (77.7)	53/74 (71.6)	N/A
Intermediate	7/8 (87.5)	N/A	N/A	N/A	N/A	N/A
Resistant	4/4 (100.0)	10/107 (9.3)	3/4 (75.0)	N/A	7/14 (50.0)	21/96 (21.9)
Klebsiella pneumoniae						
Susceptible	N/A	N/A	1/4 (25.0)	2/2 (100.0)	1/2 (50.0)	N/A
Resistant	N/A	N/A	N/A	N/A	N/A	0/1 (0.0)

Table 2.8.1.1 - Group 1.1E

Overall Success at Test of Cure by Baseline Pathogens and Susceptibility to Study Drug Received
Micro-ITT Analysis Set

	Ferry (2007)		Menday (2000)		Vik (2018)	
	Pivmecillinam 200 mg tid x 7 days (N=137) n/N1 (%)	Placebo (N=134) n/N1 (%)	Pivmecillinam 200 mg tid x 3 days (N=127) n/N1 (%)	Cephalexin 250 mg qid x 7 days (N=132) n/N1 (%)	Pivmecillinam 200 mg tid x 3 days (N=105) n/N1 (%)	Ibuprofen 600 mg tid x 3 days (N=119) n/N1 (%)
Klebsiella species						
Susceptible	3/6 (50.0)	N/A	1/2 (50.0)	0/1 (0.0)	N/A	N/A
Resistant	N/A	1/8 (12.5)	N/A	N/A	N/A	N/A
Proteus mirabilis						
Susceptible	1/1 (100.0)	N/A	6/8 (75.0)	8/12 (66.7)	N/A	N/A
Resistant	N/A	N/A	N/A	N/A	N/A	0/1 (0.0)
Gram-Positive						
Enterococcus faecalis						
Resistant	N/A	N/A	N/A	N/A	N/A	0/2 (0.0)
Enterococcus species						
Resistant	1/4 (25.0)	2/6 (33.3)	N/A	N/A	N/A	N/A
Staphylococcus aureus						
Susceptible	N/A	N/A	N/A	1/1 (100.0)	N/A	N/A
Resistant	1/2 (50.0)	0/1 (0.0)	N/A	N/A	N/A	N/A
Staphylococcus saprophyticus						
Susceptible	N/A	N/A	1/2 (50.0)	6/6 (100.0)	N/A	N/A
Resistant	1/2 (50.0)	0/6 (0.0)	3/5 (60.0)	N/A	7/12 (58.3)	4/15 (26.7)

Source: ISE Table 2.8.1.1; (Menday 2000; Ferry et al. 2007; Vik et al. 2018)

Percentages are calculated as n/N x 100.

Note: Pathogens listed as Genus "species" did not have the species identified and may include any species including the listed pathogen that has been identified to the species level

Abbreviations: ITT, intent-to-treat; micro-ITT, microbiological intent-to-treat; N, number of subjects in the micro-ITT analysis set; n, number of subjects with overall success at TOC visit; N/A, not applicable; N1, number of subjects with specified baseline pathogen and MIC; QID, four times daily; tid, three times daily; TOC, test-of-cure

Microbiological Response at TOC by Baseline Pathogen (Micro-ITT Population)

[Table 110](#) summarizes the microbiological response rates at the TOC visit for the micro-ITT analysis population in the three primary efficacy studies. Microbiological response rates in the pivmecillinam treatment groups against all baseline isolates ranged from 74.3% (Vik study), 76.4% (Menday study), and 86.9% (Ferry study).

Table 110. Microbiological Response at Test-of-Cure, Micro-ITT Analysis Set, Primary Efficacy Studies

Microbiological Response	Ferry (2007)		Menday (2000)		Vik (2018)	
	Pivmecillinam 200 mg TID x 7 days n (%)	Placebo n (%)	Pivmecillinam 200 mg TID x 3 days n (%)	Cephalexin 250 mg QID x 7 days n (%)	Pivmecillinam 200 mg TID x 3 days n (%)	Ibuprofen 600 mg TID x 3 days n (%)
N	137	134	127	132	105	119
Success	119 (86.9)	35 (26.1)	97 (76.4)	106 (80.3)	78 (74.3)	64 (53.8)
Comparison Difference	60.7		-3.9		20.5	
95% CI for the diff.	50.7, 70.8		-14.7, 6.9		7.4, 33.7	
Failure/indeterminate	18 (13.1)	99 (73.9)	30 (23.6)	26 (19.7)	27 (25.7)	55 (46.2)
Failure	8 (5.8)	86 (64.2)	18 (14.2)	16 (12.1)	27 (25.7)	55 (46.2)
Indeterminate	10 (7.3)	13 (9.7)	12 (9.4)	10 (7.6)	0 (0.0)	0 (0.0)

Source: ISA Table 2.3.1.1.1; ([Menday 2000](#); [Ferry et al. 2007](#); [Vik et al. 2018](#))

CI is calculated using the Wald method with a continuity correction.

Percentages are calculated as n/N x 100.

Abbreviations: CI, confidence interval; diff., difference; micro-ITT, microbiological intent-to-treat; N, number of subjects in the micro-ITT analysis set; n, number of subjects with microbiological success; N/A, not applicable; QID, four times daily; TID, three times daily

[Table 111](#) summarizes the microbiological success rates by baseline pathogens. Microbiological success for the predominant bacterial species, *E. coli*, ranged from 73.9% (Vik study) to 90.1% (Ferry study). In the Menday study, *P. mirabilis* was eradicated in 6/9 (66.7%) subjects compared to 8/13 (61.5%) in the cephalexin comparator. Microbiological success rates for pivmecillinam against all *Klebsiella* spp. (including *K. pneumoniae*) ranged from 50% in the Menday study, 83.3% in the Ferry study, and 100% in the Vik study. In the Vik study, *S. saprophyticus* was eradicated in 10/12 (83.3%) subjects compared to 10/15 (66.7%) in the ibuprofen group.

Table 111. Microbiological Success at Test-of-Cure by Baseline Pathogen, Micro-ITT Analysis Set, Primary Efficacy Studies

	Ferry (2007)		Menday (2000)		Vik (2018)	
	Pivmecillinam 200 mg TID x 7 days (N=137) n/N1 (%)	Placebo (N=134) n/N1 (%)	Pivmecillinam 200 mg TID x 3 days (N=127) n/N1 (%)	Cephalexin 250 mg QID x 7 days (N=132) n/N1 (%)	Pivmecillinam 200 mg TID x 3 days (N=105) n/N1 (%)	Ibuprofen 600 mg TID x 3 days (N=119) n/N1 (%)
Gram-Negative						
Enterobacteriaceae						
Citrobacter koseri	N/A	N/A	N/A	N/A	N/A	0/2 (0.0)
Citrobacter species	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)	N/A	N/A	N/A
Enterobacter species	1/2 (50.0)	3/5 (60.0)	1/1 (100.0)	1/1 (100.0)	1/3 (33.3)	2/2 (100.0)
Escherichia coli	109/121 (90.1)	21/107 (19.6)	82/104 (78.8)	87/107 (81.3)	65/88 (73.9)	52/96 (54.2)
Klebsiella pneumoniae	N/A	N/A	1/4 (25.0)	2/3 (66.7)	2/2 (100.0)	0/1 (0.0)
Klebsiella species	5/6 (83.3)	2/8 (25.0)	2/2 (100.0)	1/1 (100.0)	N/A	N/A
Proteus mirabilis	1/1 (100.0)	N/A	6/9 (66.7)	8/13 (61.5)	N/A	0/1 (0.0)
Gram-Positive						
Enterococcus faecalis	N/A	N/A	N/A	N/A	N/A	0/2 (0.0)
Enterococcus species	1/4 (25.0)	4/6 (66.7)	N/A	N/A	N/A	N/A
Staphylococcus aureus	1/2 (50.0)	0/1 (0.0)	N/A	1/1 (100.0)	N/A	N/A
Staphylococcus saprophyticus	1/2 (50.0)	3/6 (50.0)	4/7 (57.1)	6/6 (100.0)	10/12 (83.3)	10/15 (66.7)

Source: ISE Table 2.7.1.1; ([Menday 2000](#); [Ferry et al. 2007](#); [Vik et al. 2018](#))

Percentages are calculated as n/N x 100.

Note: Pathogens listed as genus "species" did not have the species identified and may include any species including the listed pathogen that has been identified to the species level

Abbreviations: ITT, intent-to-treat; micro-ITT, microbiological intent-to-treat; N, number of subjects in the micro-ITT analysis set; n, number of subjects with microbiological success at test-of-cure visit; N1, number of subjects with specified baseline pathogen.; N/A, not applicable; QID, four times daily; TID, three times daily

Antimicrobial susceptibility testing results of baseline isolates that achieved microbiological success categorized as susceptible, intermediate, and resistant are provided in the following [Table 112](#).

Table 112. Microbiological Success at Test of Cure by Baseline Pathogens and Susceptibility to Study Drug Received, Micro-ITT Analysis Set

	Ferry (2007)		Menday (2000)		Vik (2018)	
	Pivmecillinam 200 mg tid x 7 days (N=137) n/N1 (%)	Placebo (N=134) n/N1 (%)	Pivmecillinam 200 mg tid x 3 days (N=127) n/N1 (%)	Cephalexin 250 mg qid x 7 days (N=132) n/N1 (%)	Pivmecillinam 200 mg tid x 3 days (N=105) n/N1 (%)	Ibuprofen 600 mg tid x 3 days (N=119) n/N1 (%)
Gram-Negative						
Enterobacteriaceae						
<i>Citrobacter koseri</i>						
Resistant	N/A	N/A	N/A	N/A	N/A	0/2 (0.0)
<i>Citrobacter</i> species						
Susceptible	1/1 (100.0)	N/A	1/1 (100.0)	N/A	N/A	N/A
Resistant	N/A	2/2 (100.0)	N/A	N/A	N/A	N/A
<i>Enterobacter</i> species						
Susceptible	1/2 (50.0)	N/A	1/1 (100.0)	1/1 (100.0)	N/A	N/A
Resistant	N/A	3/5 (60.0)	N/A	N/A	1/3 (33.3)	2/2 (100.0)
<i>Escherichia coli</i>						
Susceptible	98/109 (89.9)	N/A	77/97 (79.4)	85/103 (82.5)	58/74 (78.4)	N/A
Intermediate	7/8 (87.5)	N/A	N/A	N/A	N/A	N/A
Resistant	4/4 (100.0)	21/107 (19.6)	3/4 (75.0)	N/A	7/14 (50.0)	52/96 (54.2)
<i>Klebsiella pneumoniae</i>						
Susceptible	N/A	N/A	1/4 (25.0)	2/2 (100.0)	2/2 (100.0)	N/A
Resistant	N/A	N/A	N/A	N/A	N/A	0/1 (0.0)
Gram-Positive						
<i>Klebsiella</i> species						
Susceptible	5/6 (83.3)	N/A	2/2 (100.0)	1/1 (100.0)	N/A	N/A
Resistant	N/A	2/8 (25.0)	N/A	N/A	N/A	N/A
<i>Proteus mirabilis</i>						
Susceptible	1/1 (100.0)	N/A	6/8 (75.0)	8/12 (66.7)	N/A	N/A
Resistant	N/A	N/A	N/A	N/A	N/A	0/1 (0.0)
<i>Enterococcus faecalis</i>						
Resistant	N/A	N/A	N/A	N/A	N/A	0/2 (0.0)
<i>Enterococcus</i> species						
Resistant	1/4 (25.0)	4/6 (66.7)	N/A	N/A	N/A	N/A
<i>Staphylococcus aureus</i>						
Susceptible	N/A	N/A	N/A	1/1 (100.0)	N/A	N/A
Resistant	1/2 (50.0)	0/1 (0.0)	N/A	N/A	N/A	N/A
<i>Staphylococcus saprophyticus</i>						
Susceptible	N/A	N/A	1/2 (50.0)	6/6 (100.0)	N/A	N/A
Resistant	1/2 (50.0)	3/6 (50.0)	3/5 (60.0)	N/A	10/12 (83.3)	10/15 (66.7)

Source: ISE Table 2.9.1.1; (Menday 2000; Ferry et al. 2007; Vik et al. 2018)

Percentages are calculated as n/N x 100.

Note: Pathogens listed as genus "species" did not have the species identified and may include any species including the listed pathogen that has been identified to the species level

Abbreviations: ITT, intent-to-treat; micro-ITT, microbiological intent-to-treat; N, number of subjects in the micro-ITT analysis set; n, number of subjects with microbiological success at test-of-cure visit; N1, number of subjects with specified baseline pathogen and susceptibility; N/A, not applicable; qid, four times daily; tid, three times daily

Correlation of Microbiological Success at TOC by Baseline MIC (Micro-ITT Population)

Please note that the in vitro susceptibilities against all baseline isolates were determined by disk diffusion, and not by agar dilution method. Therefore, the disk diffusion zone diameters were subsequently interpreted by MIC values using CLSI methodology. After a thorough review of

the Tier 2 analysis, FDA concluded that the information used for this interpretation was acceptable.

Against baseline *E. coli* isolates, the overall microbiological success rates were 83.2%, 87.5%, and 63.6% using the DD/MIC susceptible cut-off of ≥ 15 mm/ ≤ 8 μ g/mL, the intermediate cut-off of 12-14 mm/16 μ g/mL, and the resistant cut-off of ≤ 11 mm/ ≥ 32 μ g/mL, respectively ([Table 113](#)). Against baseline *P. mirabilis* isolates, the overall microbiological success of 77.8% was achieved only with the DD/MIC susceptible cut-off of ≥ 15 mm/ ≤ 8 μ g/mL. For *S. saprophyticus* the majority of isolates had MIC ≥ 32 μ g/mL and the overall microbiological success was 71.4%. To note, the FDA does not propose pivmecillinam breakpoints against *S. saprophyticus*. See [Table 113](#) for details.

Table 113. Correlation of Antimicrobial Susceptibility Testing-Cutoffs to Microbiological Success at TOC by Predominant Baseline uUTI Pathogens, Micro-ITT Analysis Set, Primary Efficacy Studies

Baseline Pathogens	DD (mm)/MIC (μ g/mL) Cut-Off	Ferry Study n1/N1(%)	Menday Study n2/N2(%)	Vik Study n3/N3(%)	Overall Categorical Microbiological Success n4/N4(%)
<i>E. coli</i>	$\geq 15/\leq 8$ (S)	98/109 (89.9)	77/97 (79.4)	58/74 (78.4)	233/280 (83.2)
	16 (I)	7/8 (87.5)	N/A	N/A	7/8 (87.5)
	≥ 32 (R)	4/4 (100)	3/4 (75)	7/14 (50)	14/22 (63.6)
<i>P. mirabilis</i>	≤ 8 (S)	1/1 (100)	6/8 (75)	N/A	7/9 (77.8)
	16 (I)	N/A	N/A	N/A	N/A
	≥ 32 (R)	N/A	N/A	N/A	N/A
<i>S. saprophyticus</i>	≤ 8	N/A	1/2 (50)	N/A	1/2 (50)
	16	N/A	N/A	N/A	N/A
	≥ 32	1/2 (50)	3/5 (60)	10/12 (83.3)	14/19 (73.7)

Source: FDA Clinical Microbiology Reviewer created table using ISE Table 2.7.1.1 and Table 2.9.1.1; ([Menday 2000](#); [Ferry et al. 2007](#); [Vik et al. 2018](#))

Note: N1, N2, N3, and N4 are the denominators in each of the categories from Ferry, Menday, Vik, and all three studies combined respectively. n1, n2, n3, and n4 are the total number of isolates in each of the categories from Ferry, Menday, Vik, and all three studies combined respectively.

Abbreviations: DD, disk diffusion; I, intermediate; MIC, minimum inhibitory concentration; micro-ITT, microbiological intent-to-treat; N/A, not applicable; TOC, test-of-cure; R, resistant; S, susceptible; uUTI, uncomplicated urinary tract infections

19.3. FDA Recommendations for Breakpoints or Susceptibility Test Interpretive Criteria

The following is a summary of the Agency's breakpoints recommendations with rationale for labeling recommendations on the first and the second list pathogens pertinent to Section 12.4 Microbiology of the pivmecillinam labeling:

1st List/Indicated Pathogens for the uUTI Indication

FDA recommends including the following uropathogens on the first list:

- Aerobic Gram-Negative Bacteria
 - *Escherichia coli*
 - *Proteus mirabilis*
- Aerobic Gram-Positive Bacteria
 - *S. saprophyticus*

MEC has been shown to be active against most isolates of the above pathogens, both in vitro and in clinical infections from the three primary efficacy studies. The in vitro activity of MEC was determined using the MIC data of isolates from the US surveillance and from the published reports.

There were no MIC data for *S. saprophyticus* isolates in the clinical studies, but the pathogen was included in the 1st list based on favorable clinical and microbiological response in the primary efficacy studies and because it was the second most predominant pathogen after *E. coli* in the clinical studies.

2nd List/In Vitro Pathogens Associated With the uUTI Indication

The second list includes bacteria whose pivmecillinam MIC₉₀ was provided and was less than or equal to the FDA recommended susceptible pivmecillinam breakpoint of ≤8 µg/mL against isolates of similar genus or organism group that were included on the first list. However, the efficacy of pivmecillinam in treating clinical infections caused by the second list bacteria has not been established in adequate and well-controlled clinical trials.

- Aerobic Gram-Negative Bacteria
 - *Citrobacter freundii*
 - *Enterobacter cloacae*
 - *Klebsiella pneumoniae*
 - *Klebsiella aerogenes*
 - *Klebsiella oxytoca*

Agency's MIC and DD STIC/Breakpoints Recommendations With Rationales

The Agency's recommended agar dilution MIC and DD breakpoints for MEC against *E. coli*, and *P. mirabilis* are listed in [Table 114](#).

Table 114. Agency's Recommended MIC and DD STIC/Breakpoints for Mecillinam

uUTI Indicated Pathogens	Agar Dilution MIC (µg/mL)			Disk Diffusion Zone Diameter (mm)		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
<i>E. coli</i>	≤8	16	≥32	≥15	12-14	≤11
<i>P. mirabilis</i>	≤8	16	≥32	≥15	12-14	≤11

Source: Clinical Microbiology Reviewer created table.

Abbreviations: DD, disk diffusion; MIC, minimum inhibitory concentration; STIC, susceptibility testing interpretive criteria

The Agency's breakpoints determination primarily relies on clinical and microbiological response data in the efficacy studies as well as on in vitro MIC₉₀ values of clinical isolates from the US surveillance studies and from published reports.

In addition, the Agency relied on the data presented by the Applicant to CLSI (formerly NCCLS) subcommittee on antimicrobial susceptibility testing at the June 2000 meeting for including MEC breakpoints in the M100 document to inform the evaluation of the correlation between zone diameter inhibition and MIC values. These data were submitted to the NDA in response to FDA IRs for facilitating the Agency's breakpoints recommendations.

The Agency identifies susceptible (S)/ intermediate (I)/ resistant (R) [S/I/R] DD breakpoints of ≥ 15 mm/12-14 mm/ ≤ 11 mm and agar dilution MIC breakpoints of $\leq 8/16/\geq 32$ µg/mL for *E. coli*, and *P. mirabilis*. These breakpoints will cover nearly all Enterobacterales isolates (>90%) from 2018-2020 surveillance study and from published studies. Against 3,303 Enterobacterales surveillance isolates, the MIC₅₀/MIC₉₀ of mecillinam was 0.25/4 µg/mL with an MIC range of ≤ 0.015 to >128 µg/mL. Against 1869 *E. coli* and 307 *P. mirabilis* surveillance isolates, the MIC₅₀/MIC₉₀ values were 0.25/2 µg/mL (97.5% susceptible) and 0.5/16 µg/mL (87.3% susceptible) respectively.

The microbiological success was evaluated using DD/MIC cut-offs of ≥ 15 mm/ ≤ 8 µg/mL, 12-14 mm/16 µg/mL, and ≤ 11 mm/ ≥ 32 µg/mL, corresponding to the CLSI/EUCAST breakpoints of susceptible, intermediate, and resistant, respectively. At TOC, against baseline *E. coli* isolates, the overall microbiological success rates were 83.2%, 87.5%, and 63.6% using the DD/MIC susceptible cut-off of ≥ 15 mm/ ≤ 8 µg/mL, the intermediate cut-off of 12-14 mm/16 µg/mL, and the resistant cut-off of ≤ 11 mm/ ≥ 32 µg/mL respectively ([Table 113](#)). Against baseline *P. mirabilis* isolates, the overall microbiological success of 77.8%; all isolates had DD/MIC of ≥ 15 mm/ ≤ 8 µg/mL. The microbiological success of baseline isolates was evaluated using the CLSI/EUCAST DD susceptible cut-off of ≥ 15 mm that corresponds to MIC breakpoint of ≤ 8 µg/mL.

Microbiological response for isolates with DD/MIC of ≤ 11 mm/ ≥ 32 µg/mL was less favorable, thus supporting the resistant breakpoint of ≤ 11 mm/ ≥ 32 µg/mL. The small number of isolates with DD/MIC of 12-14 mm/16 µg/mL and the fact that all isolates were observed only in one study (Ferry study), limited the interpretation of outcomes associated with these isolates. Consequently, the cut-off of 12-14 mm/16 µg/mL was determined as the intermediate breakpoint; this category also provides a buffer zone for inherent variability in test methods. The DD/MIC cut-off of ≥ 15 mm/ ≤ 8 µg/mL was determined as a susceptible breakpoint. Of note, the susceptible and resistant breakpoints correspond to those established by EUCAST and CLSI.

20. Mechanism of Action / Drug Resistance

20.1. Mechanism of Action

See Section [5.3](#) Clinical Microbiology-Mechanism of Action.

20.2. Drug Resistance

Mechanism of Resistance - Spontaneous Mutation Frequency

The frequencies of in vitro resistance mutations to MEC observed in *E. coli* varied from 8×10^{-8} to 2×10^{-5} per cell when exposed to 32-256 times MIC ([Thulin et al. 2015](#)).

Resistance mutations selected in the laboratory affect many different cellular functions, including the following:

- Cell elongation and cell division
- Cellular amino acid levels and tRNA synthetases
- Composition of lipopolysaccharide
- The regulatory system that controls, e.g., capsule production and cell division
- Cysteine biosynthesis

Though *E. coli* mutants were generated in vitro, many of these mutants showed large reductions in fitness, suggesting that despite the high frequency of mutations to resistance in vitro, resistance development remains low in clinical settings because most of these mutants grow too slowly to be stably maintained. Among all the mutant types found in vitro, only a small subset were fit enough to be stably maintained in the bladder. These surviving mutants showed mutations in the CysB gene encoding for the CysB protein, the major positive regulator of the cysteine biosynthesis pathway. Turning this pathway off confers MEC resistance, but only in growth media low in cysteine.

Molecular Characterization of the Resistant Strains From Surveillance Studies

MEC resistant (MIC > 8 mg/L) *E. coli* and *K. pneumoniae* isolates from the surveillance studies (2018-2020) were characterized genotypically to analyze their resistance profile. Resistance mechanisms to MEC were different between *E. coli* and *K. pneumoniae*. While resistance in *K. pneumoniae* was associated with MEC target gene modification, i.e., mutations in PBP-2, resistance in *E. coli* involved mainly inactivation of CysB and LpoB, a penicillin-binding protein activator, rendering nonessential to the MEC target.

Resistance in *E. coli* involved inactivation of helix-turn-helix (HTH-type) transcriptional regulator (CysB), and penicillin-binding protein activator (LpoB) or PBP-1b. Out of the 46 MEC nonsusceptible *E. coli* isolates, only one isolate showed mutations in the MEC target PBP-2.

MEC-resistance mechanisms in *K. pneumoniae* differ from the mechanisms observed in *E. coli*. All but one of the 45 MEC-resistant *K. pneumoniae* isolates showed mutations in MEC target PBP-2, and half of these isolates showed mutations in PBP-1. Furthermore, only one *K. pneumoniae* had an alteration in LpoB.

Substantial use of pivmecillinam over several decades in countries where it is licensed for the treatment of UTI has not resulted in an increased incidence of MEC-resistant *E. coli* or other gram-negative organisms ([Kahlmeter and Eco.Sens 2003](#); [Kahlmeter and Poulsen 2012](#); [Kahlmeter et al. 2015](#)). This may be attributable to MEC-resistant isolates having significantly

reduced fitness compared with wildtype isolates, unlike other antimicrobials ([Sommer et al. 2017](#)).

21. Other Drug Development Considerations

Not Applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

The Office of Scientific Investigations (OSI) conducted an inspection of Utility Therapeutics, Ltd, focusing on a review of Protocol MET-9401 (the Ferry study). Notable findings included changes Utility made to the legacy dataset that was transferred to them from Leo Pharma, the original sponsor of Protocol MET 940, following source data verification by Utility for randomly selected subjects. After the inspection, each of the data changes were reviewed and verified against the original scanned copies of the CRFs for the affected subjects and no discrepancies were noted. Furthermore, none of the data changes appear to impact the individual subject's overall response assessment (i.e., success, failure, or indeterminate) at the TOC visit or inclusion in or exclusion from the micro-ITT analysis set.

OSI also found a lack of audit trails available for their review and therefore OSI was unable to ensure that no other changes were made to the data beyond those identified by Utility in their listing of changes. In a March 4, 2024, IR response, Utility explained that the data changes incorporated directly into the ADaM datasets created by them and a formal audit trail to track the data changes was not available. In addition, Utility noted difficulty in comparing the original legacy study data received from Leo Pharma to the ADaM dataset.

OSI's assessment was that the lack of audit trails and comparability between the legacy and ADaM datasets for the Ferry study made it difficult to verify whether additional changes were made to study data beyond those identified by the Applicant. OSI deferred to the Division of Anti-Infectives regarding whether the absence of audit trails for the Ferry study affected assessment of overall efficacy and safety for the NDA.

The NDA review team reviewed and discussed the inspectional findings with OSI. The review team noted that investigator site inspections had been conducted during the FDA's previous NDA review of [REDACTED] ^{(b) (4)} and those inspections did not reveal issues that would affect conclusions on safety or efficacy data. In addition, given the totality of the nonclinical and clinical evidence provided in this NDA, including the consistent findings on safety and efficacy of pivmecillinam administered to female subjects 18 years of age or older with uUTI across numerous multicenter, randomized, controlled studies conducted in Europe, the US and Canada, as well as postmarketing data that have not revealed any novel or unexpected safety findings, the review team concluded that available evidence supports the safety and efficacy of pivmecillinam for the approved indication.

23. Labeling: Key Changes and Considerations

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI submitted on October 24, 2023 (see [Table 115](#) below). The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 115. Key Labeling Changes and Considerations

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to the Applicant's Draft PI
BOXED WARNING	Not Applicable
1 INDICATIONS AND USAGE	This section was modified to limit the indication to female patients 18 years and older with uncomplicated urinary tract infections (uUTI) because male patients are considered to have complicated UTIs (cUTIs). Refer to Section 6 of the IAMA for additional details. The susceptible microorganisms were changed to delete (b) (4) and insert <i>Escherichia coli</i>, <i>Proteus mirabilis</i> and <i>S. saprophyticus</i> based on supporting in vitro and clinical data. Refer to Section 19 of the IAMA for additional details.
2 DOSAGE AND ADMINISTRATION	A sentence was added to indicate that PIVYA may be taken with or without food. In subsection 2.1 Recommended Dosage of the PI and to be consistent with the labeling recommendations in the Guidance for Industry: Dosage and Administration section of Labeling for Human Prescription Drug and Biological Product-Content and Format. Refer to Section 8.2.1 and 14 of the IAMA for additional details. In subsection 2.1 of the PI, the Applicant's proposed (b) (4) was removed because such adjustments are not adequately supported by the provided clinical pharmacology information. Refer to Section 8.1.1.1 and 14 of the IAMA for additional details. Specific instructions to take a missed dose was added in subsection 2.2 Recommendations Regarding Missed Doses of the PI. Refer to Section 14 of the IAMA for additional details.
4 CONTRAINDICATIONS	The contraindications Section 4 of the PI was revised to be consistent with the Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of the Labeling guidance (e.g., "DRUG-X is contraindicated in patients with Condition-Y" instead of "DRUG-X should not be used in patients with Condition-Y"). In subsection 4.2 of the PI, the Applicant's proposed contraindication statement for carnitine deficiency was modified to include secondary carnitine deficiency due to inborn errors of metabolism. Refer to Section 7.7.1 of the IAMA for additional details.

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to the Applicant's Draft PI
5 WARNINGS AND PRECAUTIONS	Section 5, Warnings and Precautions of the PI was revised to include risk mitigation information as appropriate. Refer to the labeling guidance. Additionally, the subsection titled "Severe Cutaneous Adverse Reactions" was moved up from subsection 5.8 to subsection 5.2 to reflect its relative clinical significance. These revisions are consistent with the labeling recommendations in the Guidance for Industry: Warnings and Precautions, Contraindications and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format. In Subsection 5.3, Carnitine Depletion, of the PI, the wording was modified to add other patient populations at risk for symptomatic reductions in serum carnitine, such as those with renal impairment or decreased muscle mass as well as risk mitigation. Refer to Section 7.7.1 of the IAMA for additional details. Subsection 5.7 Interference with Newborn Screening Test was revised to remove (b) (4) (b) (4) . Refer to the Division of Pediatric and Maternal Health (DPMH-02) Pediatric Review in DARRTS (dated 3/6/2024) for additional details.
6 ADVERSE REACTIONS	In subsection 6.1 of the PI, the Applicant's table was deleted and a new table for Trial 1 (based on data from Ferry) was inserted as it provided a more complete assessment of adverse reactions. Dosage was moved to a footnote in the table to be consistent with the approved dose of 200 mg three times a day. In subsection 6.2 of the PI, "(b) (4)", "(b) (4)", and "(b) (4)" were deleted because they were already included in subsection 6.1 Clinical Trials Experience, of the PI. Refer to Section 7 of the IAMA for additional details on the rationale for labeling changes made to subsections 6.1 and 6.2 of the PI.
7 DRUG INTERACTIONS	Applicant's proposed (b) (4) was removed from Section 7 of the PI because (b) (4) (b) (4) Refer to Section 14 of the IAMA for additional details. Subsection 7.3 Drug Interference with Newborn Screening Test was added to the PI to provide practical guidance on the interference of PIVYA with a newborn screening test as per the labeling recommendations in 21 CFR 201.57 (c)(8). Refer to the DPMH-02 Pediatric Review in DARRTS (dated 3/6/2024) for additional details.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential,	Risk summary in subsection 8.1 Pregnancy of the PI was modified to include available animal data on reproduction and developmental toxicity with pivmecillinam and mecillinam, including

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to the Applicant's Draft PI
Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	safety margins to the maximum recommended human dose (MRHD). Refer to Section 13 of the IAMA for additional details. The descriptions of the animal studies and findings under Animal Data in subsection 8.1 of the PI were expanded to include more detail with calculated safety margins to the MRHD based on body surface area comparisons. Refer to Section 13 of the IAMA for additional details. In subsection 8.1 of the PI, the Applicant's proposed text regarding (b) (4) was removed because (b) (4). Refer to Section 8.4 of the IAMA and the DPMH-03 Maternal Health Review in DARRTS (dated 3/20/2024) for additional details. PLR/PLLR compliant language was added to subsection 8.2 Lactation indicating that when a drug is present in animal milk, it is likely to be present in human milk. Applicant's proposed (b) (4) in subsection 8.2 of the PI was removed because (b) (4). Refer to Section 8.4 and Section 13 of the IAMA and the DPMH-03 Maternal Health Review in DARRTS (dated 3/20/2024) for additional details. Subsection 8.4 Pediatric Use was modified to include the risk of significant hypocarnitinemia in young pediatric patients 1 year of age or less as well as risk mitigation information. Refer to Section 7.7.1 of the IAMA for additional details. Interference with Newborn Screening Test information was added to subsection 8.4 of the PI. Refer to the DPMH-02 Pediatric Review in DARRTS (dated 3/6/2024) for additional details. Subsection 8.5 was modified to present the population 65 years and older and 75 years of age and older in the safety studies included in Section 6 (Studies 1, 2, and 3) and in the efficacy studies included in Section 14 (Studies 1,2, and 4). This is consistent with the labeling recommendations in the Guidance for Industry: Geriatric Information in Human Prescription Drug and Biological Product Labeling. Refer to Section 16 and 17 of the IAMA for additional details. In subsection 8.7 Renal Impairment, the Applicant's proposed (b) (4) was deleted due to (b) (4). Refer to Section 14.2.7 of the IAMA for additional details.
9 DRUG ABUSE AND DEPENDENCE	Not Applicable

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to the Applicant's Draft PI
12 CLINICAL PHARMACOLOGY	Subsection 12.4 Microbiology of the PI has been revised for clarity as follows: Some sentences were deleted from 'Mechanism of Action', 'Resistance', 'Antimicrobial Activity', and 'Susceptibility Testing' because they are not relevant to that section. The 1st list and 2nd list pathogens were revised based on the data submitted in the NDA. Refer to Section 19 Clinical Microbiology of the IAMA for additional details regarding the Microbiology labeling changes described above.
13 NONCLINICAL TOXICOLOGY	Descriptions of the results of the in vitro and in vivo genotoxicity studies in subsection 13.1 of the PI were modified to simplify the language. Similarly, descriptions of the animal fertility studies in subsection 13.1 were simplified and the safety margins to the MRHD were included. (b) (4)
14 CLINICAL STUDIES	Refer to Section 13 of the IAMA for additional details. For the studies described in section 14 of the PI, additional details were added to summarize demographic and patient characteristics, baseline pathogens, the definition of the micro-ITT analysis set in which efficacy results were presented, and definitions for clinical, microbiological, and overall response endpoints. Refer to Section 6 of the IAMA for additional information. (b) (4) was removed because (b) (4) . Refer to Section 6 of the IAMA for additional information.
17 PATIENT COUNSELING INFORMATION	The Applicant's proposed (b) (4) was removed from the Patient Counseling Information section as per the labeling recommendations in the Guidance for Industry: Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products-Content and Format. Added a Missed Dose section to Section 17 of the PI based on the changes made to subsection 2.2 of the PI above.

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to the Applicant's Draft PI
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Several labeling revisions have been recommended in the Product Quality related sections (3 Dosage Forms and Strengths, 11 Description, 16 How Supplied/Storage and Handling) of the Prescribing information (PI) (e.g., properly displaying the drug product name and strength along with the salt equivalency statement and changes to the blister sheet labeling (e.g., proposing an additional pack size of 1 blister sheet with 9 tablets). Refer to the Office of Quality Products Review in DARRTS (dated 3/19/2024).

Source: FDA Reviewer
¹ Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
² For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviations: cUTI, complicated urinary tract infection; PI, Prescribing Information

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Carton labeling
- Container labeling

24. Postmarketing Requirements and Commitments

1. Conduct an open-label single-dose safety, tolerability and pharmacokinetic study in pediatric subjects less than 12 years of age receiving systemic antibacterial therapy for the treatment of a suspected or confirmed bacterial infection.

Draft Protocol Submission: August 2024
Final Protocol Submission: December 2024
Study Completion: February 2028
Final Report Submission: August 2028

2. Conduct a multicenter, randomized, single-blind study to evaluate the safety and tolerability of pivmecillinam hydrochloride versus nitrofurantoin for the treatment of pediatric subjects, 12 years to less than 18 years of age, with uncomplicated urinary tract infections.

Draft Protocol Submission: July 2024
Final Protocol Submission: November 2024
Study Completion: May 2026
Final Report Submission: November 2026

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3. Conduct a multicenter, randomized, single-blind study to evaluate the safety and tolerability of pivmecillinam hydrochloride versus an appropriate comparator for the treatment of pediatric subjects, 2 months to less than 12 years of age, with uncomplicated urinary tract infections.

Draft Protocol Submission: December 2028
Final Protocol Submission: March 2029
Study Completion: July 2030
Final Report Submission: January 2031

4. Conduct a U.S. surveillance study over a five-year period after the introduction of pivmecillinam to the market to determine if resistance or decreased susceptibility to pivmecillinam is occurring in the target population of bacteria that are in the approved pivmecillinam label.

Draft Protocol Submission: September 2024
Final Protocol Submission: December 2024
Study Completion: June 2030
Interim Report Submission: August 2026; August 2027; August 2028; August 2029
Final Report Submission: August 2030

5. Conduct a lactation study (milk only) in lactating women who have received pivmecillinam to assess concentrations of pivmecillinam in breast milk using a validated assay and to assess the effects on the breastfed infant.

Draft Protocol Submission: July 2024
Final Protocol Submission: November 2024
Study Completion: November 2025
Final Report Submission: May 2026

PMC (CMC/Product Quality)

4. Conduct studies and generate data to finalize the regulatory dissolution specification (method and acceptance criterion) for the drug product (pivmecillinam tablets, 185 mg) to be used at batch release and for stability studies.

Interim Report: 10/2024
Final Report: 05/2025

25. Financial Disclosure

Table 116. Covered Clinical Studies: Bresky 1977, Ferry 2007, Hansen 1981, Menday 2000, Nicolle 2002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 421 (Note: some appear to be duplicates with the same names but different addresses)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None reported.		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None reported.		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Not Applicable (NA). Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements: NA	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: NA	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): >400 listed		
Is an attachment provided with the reason: Financial Disclosure information was not available for all clinical investigators. Applicant stated that "the covered clinical studies were mostly conducted prior to 21 CFR Part 54 and 21 CFR Part 312 coming into effect, and the reports include very little investigator information...UTILITY Therapeutics, Ltd. Sent up to 2 letters, 1 email and made up to 2 phone calls to obtain this information wherever possible."	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

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Guidance for Industry

FDA Guidance for Industry *Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment* (August 2019)

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27. Review Team

Table 117. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Joseph Nguyen
Chief, regulatory project management staff	Gregory DiBernardo
Nonclinical reviewer	Amy Ellis
Nonclinical team leader	Amy Nostrandt
Microbiology reviewer	Jalal Sheikh
Microbiology team leader	Avery Goodwin
OCP reviewer(s)	Timothy Bensman
OCP team leader(s)	Abhay Joshi
Pharmacometrics reviewer	Jiajun Liu
Pharmacometrics team leader	Justin Earp
Clinical reviewer	Leslie Ball
Clinical team leader	Mayurika Ghosh
Biometrics reviewer	Fraser Smith; Saahithi Rao
Biometrics secondary reviewer	Daniel Rubin
Cross-disciplinary team leader	Mayurika Ghosh
Division director (pharm/tox)	Hanan Ghantous
Deputy Division director (OCP)	Zhixia Danielsén
Division director (OB)	Nie Lei
Associate Director for Labeling (DAI)	Abimbola Adebawale
Division director (clinical)	Peter Kim
Deputy division director (clinical)	Dmitri Iarikov
Director regulatory project management staff, (DRO-ID),	Maureen Dillon Parker

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 118. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Jessica Zarenkiewicz; Dorota Matecka (TL)
OPDP	Qumerunnisa Syed
OSI	Cheryl Grandinetti; Phillip Kronstein (TL)
OSE/DEPI	Ikponmwosa Osaghae; Yan Li (TL)
OSE/DMEPA	Kristine Needleman; Valerie Vaughn (TL)
DPMH (Maternal Health Review)	Kristie Baisden; Tamara Johnson (TL)
DPMH (Pediatric Review)	Sonaly McClymont; Shetarra Walker (TL)

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatric and Maternal Health; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; TL, Team Leader

27.1. Reviewer Signatures

Table 27-119 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Timothy Bensman OCP DIDP	Sections: 5, 6, 8, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Timothy Bensman		Digitally signed by Timothy Bensman Date: 4/23/2024 5:02 PM EDT GUID: 202442321216		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Timothy Bensman OCP DIDP	Sections: 5,6,8,14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Timothy Bensman		Digitally signed by Timothy Bensman Date: 4/23/2024 5:03 PM EDT GUID: 20244232132		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Microbiology Discipline Primary Reviewer	Jalal Sheikh OID DAI	Sections: 5.3; 19; and 20	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Jalal Sheikh Digitally signed by Jalal Sheikh Date: 4/23/2024 5:04 PM EDT GUID: 202442321435				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Mayurika Ghosh OID DAI	Sections: 2, 3.1, 4, 7, 8.3, 8.4, 10, 17, 21, 22	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Mayurika Ghosh Digitally signed by Mayurika Ghosh Date: 4/23/2024 5:07 PM EDT GUID: 202442321735				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Gregory Dibernardo ORO DROID	Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Gregory Dibernardo Digitally signed by Gregory Dibernardo Date: 4/23/2024 5:07 PM EDT GUID: 202442321738				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Tertiary Reviewer	Abimbola Adebawale OID DAI	Sections: 23, 23.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Abimbola Adebawale Digitally signed by Abimbola Adebawale Date: 4/23/2024 5:28 PM EDT GUID: 202442321280				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Abimbola Adebawale OID DAI	Sections: 23, 23.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Abimbola Adebawale Digitally signed by Abimbola Adebawale Date: 4/23/2024 5:28 PM EDT GUID: 2024423212824				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Abimbola Adebawale OID DAI	Sections: 23, 23.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Abimbola Adebawale Digitally signed by Abimbola Adebawale Date: 4/23/2024 5:28 PM EDT GUID: 2024423212850				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Daniel Rubin OB DBIV	Sections: 6, 15, 16, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Daniel Rubin Digitally signed by Daniel Rubin Date: 4/23/2024 5:29 PM EDT GUID: 202442321297				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Abhay Joshi OCP DIDP	Sections: 5.1, 5.2, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Abhay Joshi Digitally signed by Abhay Joshi Date: 4/23/2024 5:43 PM EDT GUID: 2024423214350				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Zhixia Danielsen OCP DIDP	Sections: 5.1, 5.2, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3, 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Zhixia Danielsen Digitally signed by Zhixia Danielsen Date: 4/23/2024 5:59 PM EDT GUID: 2024423215923				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Fraser Smith OB DBIV	Sections: 6, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Fraser Smith Digitally signed by Fraser Smith Date: 4/23/2024 6:02 PM EDT GUID: 202442322232				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Tertiary Reviewer	Maureen Dillon Parker ORO DROID	Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Maureen Dillon Parker Digitally signed by Maureen Dillon Parker Date: 4/23/2024 6:12 PM EDT GUID: 2024423221237				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Lei Nie OB DBIV	Sections: 6, 15-16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Lei Nie Digitally signed by Lei Nie Date: 4/23/2024 6:15 PM EDT GUID: 2024423221543				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Primary Reviewer	Dorota Matecka OPQAI DPQAI	Sections: 9, 23, 24	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Signing on behalf of the OPQ Review Team
Signature: Dorota Matecka Digitally signed by Dorota Matecka Date: 4/23/2024 8:11 PM EDT GUID: 202442401110				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Dorota Matecka OPQAI DPQAI	Sections: 9, 23, 24	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Signing on behalf of the OPQ Review Team
Signature: Dorota Matecka Digitally signed by Dorota Matecka Date: 4/23/2024 8:11 PM EDT GUID: 202442401149				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Joseph Nguyen ORO DROID	Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Joseph Nguyen		Digitally signed by Joseph Nguyen Date: 4/23/2024 8:57 PM EDT GUID: 202442405759		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Microbiology Discipline Secondary Reviewer	Avery Goodwin OID DAI	Sections: 5.3, 19 and 20	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Avery Goodwin		Digitally signed by Avery Goodwin Date: 4/24/2024 6:03 AM EDT GUID: 202442410318		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Hanan Ghantous OID DPTID	Sections: 7.1,13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hanan Ghantous Digitally signed by Hanan Ghantous Date: 4/24/2024 8:39 AM EDT GUID: 2024424123913				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Other	Saahithi Rao OB DAI	Sections: Section 6.2.1, 6.2.2, 6.2.3, 6.2.4, 6.3.1, 6.3.3, 16.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Saahithi Rao Digitally signed by Saahithi Rao Date: 4/24/2024 8:40 AM EDT GUID: 202442412407				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Leslie Ball OID DAI	Sections: 1-8, 10,17, 23-26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Leslie Ball Digitally signed by Leslie Ball Date: 4/24/2024 8:52 AM EDT GUID: 2024424125232				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Jiajun Liu OCP DPM	Sections: 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jiajun Liu Digitally signed by Jiajun Liu Date: 4/24/2024 9:22 AM EDT GUID: 2024424132242				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Amy Ellis OID DPTID	Sections: 7.1, 8.4 (Animal Data), 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Amy Ellis Digitally signed by Amy Ellis Date: 4/24/2024 9:27 AM EDT GUID: 2024424132710				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Supervisor / Team Lead	Justin Earp OCP DPM	Sections: 5.2, 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Justin Earp Digitally signed by Justin Earp Date: 4/24/2024 9:38 AM EDT GUID: 202442413388				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Amy Nostrandt OID DPTID	Sections: 7.1, 8.4, 13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Amy Nostrandt Digitally signed by Amy Nostrandt Date: 4/24/2024 10:33 AM EDT GUID: 202442414330				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Tertiary Reviewer	Dmitri Iarikov OID DAI	Sections: I, II, and III	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Dmitri Iarikov Digitally signed by Dmitri Iarikov Date: 4/24/2024 11:13 AM EDT GUID: 2024424151320				

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MAYURIKA GHOSH
04/23/2024 05:17:11 PM

PETER W KIM
04/24/2024 11:18:08 AM